APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Resubmission	Previous CIRM Funding	Disease Indication	Product Type	Approach
DISC2-13212	Preclinical development of an exhaustion-resistant CAR-T stem cell for cancer immunotherapy	**$1,420,200**	**Y**	**100**	99	3	90	100	15	0	Y	N	Bone cancer	Cell and gene therapy	Engineer exhaustion-resistant CAR T cells to provide more presistant anti-cancer activity
DISC2-13051	Generating deeper and more durable BCMA CAR T cell responses in Multiple Myeloma through non-viral knockin/knockout multiplexed genome engineering	**$1,463,368**	**Y**	**90**	90	3	84	94	13	1	N	N	Blood cancer - Multiple Myeloma	Cell and gene therapy	Engineer CAR T cells to ablate RASA2, which suppresses anti-cancer activity
DISC2-13020	Injectable, autologous iPSC-based therapy for spinal cord injury	**$789,000**	**Y**	**90**	90	0	89	91	12	0	N	Y	Spinal cord injury	Cell therapy	Transplant iPSC-derived corticol neuron progenitors to regenerate SC cells
DISC2-13009	New noncoding RNA chemical entity for heart failure with preserved ejection fraction.	**$1,397,412**	**Y**	**90**	89	2	85	90	15	0	Y	Y	Heart failure	Biologic	Reduce macrophage-mediated inflammation and fibrosis in injured heart tissue
DISC2-13232	Modulation of oral epithelium stem cells by RSpo1 for the prevention and treatment of oral mucositis	**$942,050**	**Y**	**88**	88	4	85	95	14	0	Y	N	Radiation-induced oral injury	Biologic	Protect or repair oral tissue via activation of endogenous Lgr5+ stem cells
DISC2-13077	Transplantation of genetically corrected iPSC-microglia for the treatment of Sanfilippo Syndrome	**$1,199,922**	**Y**	**87**	86	2	83	88	12	1	N	Y	Sanfilippo Syndrome	Cell and gene therapy	Engineer microglia to provide a replacement source of SGSH in the brain
DISC2-13201	Matrix Assisted Cell Transplantation of Promyogenic Fibroadipogenic Progenitor (FAP) Stem Cells	**$1,179,478**	**Y**	**87**	85	3	75	87	11	2	Y	N	Rotator cuff injury	Cell therapy	Reprogram muscle stem cells to an adipogenic progenitor that promotes regeneration of skeletal muscle
DISC2-13063	Improving the efficacy and tolerability of clinically validated remyelination-inducing molecules using developable combinations of approved drugs	**$1,554,126**	**Y**	**86**	86	2	85	90	14	0	N	Y	Multiple sclerosis	Small molecule	Promote remyelination by targeting the immune-depleted population of glial stem cells
DISC2-13213	Extending Immune-Evasive Human Islet-Like Organoids (HILOs) Survival and Function as a Cure for T1D	**$1,523,285**	**Y**	**86**	86	1	85	88	14	0	Y	Y	Type 1 Diabetes	Biologic	Transplant glucose-responsive, immune-shielded, human islet-like organoids
DISC2-13136	Meniscal Repair and Regeneration	**$1,620,645**	**Y**	**86**	86	0	85	86	13	0	Y	Y	Meniscal injury	Cell therapy	Transplant clonal hESC-derived MSC to provide more consistent and potent cartilage repair
DISC2-13072	Providing a cure for sphingosine phosphate lyase insufficiency syndrome (SPLIS) through adeno-associated viral mediated SGPL1 gene therapy	**$1,463,400**	**Y**	**85**	86	4	80	93	11	4	N	N	SPLIS	Gene therapy	Deliver SGPL1 to kidney cells to restore lipid metabolism and modify disease
DISC2-13205	iPSC-derived smooth muscle cell progenitor conditioned medium for treatment of pelvic organ prolapse	**$1,420,200**	**Y**	**85**	85	0	85	85	14	0	N	Y	Pelvic organ prolapse	Biologic	Increase myogenesis in the vaginal wall to restore tissue integrity
DISC2-13102	RNA-directed therapy for Huntington's disease	**$1,408,923**	**Y**	**85**	85	1	83	87	11	1	N	N	Huntington's Disease	Gene therapy	Deliver a nuclease transgene targeting the toxic RNA causative of Huntington's disease
DISC2-13131	A Novel Therapy for Articular Cartilage Autologous Cellular Repair by Paste Grafting	**$1,316,215**	**Y**	**85**	84	5	65	88	14	1	N	N	Joint degeneration and injury	Biologic	Implant a MSC-containing paste graft to repair joint cartilage
DISC2-13013	Optimization of a gene therapy for inherited erythromelalgia in iPSC-derived neurons	**$1,157,313**	**Y**	**85**	84	4	78	95	7	6	N	N	Inherited Erythromelalgia	Gene therapy	Repair the overactive mutant sodium channel that is causative of inherited erythromelalgia
DISC2-13221	Development of a novel stem-cell based carrier for intravenous delivery of oncolytic viruses	**$899,342**	**Y**	**85**	83	4	75	85	7	7	N	N	Metastatic breast cancer	Cell therapy	Engineer enucleated MSC to efficiently and safely deliver oncolytic virus to disseminated cancer cells
DISC2-13163	iPSC Extracellular Vesicles for Diabetes Therapy	**$1,354,928**	**N**	**84**	84	1	82	86	6*	9	Y	N			
DISC2-13217	An hematopoietic stem-cell-based approach to treat HIV employing CAR T cells and anti-HIV broadly neutralizing antibodies.	**$1,143,600**	**N**	**84**	83	2	80	86	2	13	Y	N			
DISC2-13056	Developing recombinant AAV-based gene therapy for dominant optic atrophy caused by OPA1 mutations	**$1,316,259**	**N**	**82**	81	2	75	83	0	13	N	N			
DISC2-13150	Novel methods to eliminate cancer stem cells	**$1,384,347**	**N**	**81**	80	3	75	83	0	12	N	N			

APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Resubmission	Previous CIRM Funding	Disease Indication	Product Type	Approach
DISC2-13191	Key Tools for Spermatogonial Stem Cell Therapy	**$780,180**	**N**	**80**	81	4	70	86	4	10	Y	N			
DISC2-13091	Enabling activity-dependent maturation of iPSC-derived neurons using graphene-mediated long-term optical stimulation	**$675,000**	**N**	**80**	81	2	80	85	2	13	N	N			
DISC2-13035	Reversal of dysregulated myelopoiesis in breast cancers to boost antitumor immunotherapy	**$1,397,000**	**N**	**80**	81	2	80	85	1	12	N	N			
DISC2-13024	Modified RNA-Based Gene Therapy for Cardiac Regeneration Through Cardiomyocyte Proliferation	**$1,565,784**	**N**	**80**	80	2	80	86	1	13	N	N			
DISC2-13016	Treatment of Myasthenic Syndrome due to Choline Acetyltransferase Deficiency Using AAV9-mediated Gene Therapy	**$752,102**	**N**	**80**	80	2	75	82	0	15	N	N			
DISC2-13042	Engineered Human Stem Cell-Derived Pancreatic Islets Encapsulated in a Thin Film Device for Patients with Type 1 Diabetes	**$1,459,018**	**N**	**80**	80	0	80	80	0	14	N	Y			
DISC2-13045	Development of small molecules to restore function in neurons from Intellectual Disability Syndromes	**$1,404,000**	**N**	**80**	80	3	75	84	0	13	Y	N			
DISC2-13068	Gene therapy vector correcting endoplasmic reticulum stress and GABA uptake defect in myoclonic atonic epilepsy	**$1,283,566**	**N**	**80**	80	1	80	82	0	13	N	N			
DISC2-13186	Novel antisense therapy to treat genetic forms of neurodevelopmental disease	**$1,056,000**	**N**	**80**	80	1	75	80	0	14	N	Y			
DISC2-13206	A new precision medicine based iPSC-derived model to study personalized intestinal fibrosis treatments in pediatric patients with Crohn's disease	**$776,340**	**N**	**80**	80	1	80	82	0	15	N	N			
DISC2-13122	Drug Development of Inhibitors of Inflammation Using Human iPSC-Derived Microglia (hiMG)	**$1,648,670**	**N**	**80**	79	3	75	85	1	12	N	N			
DISC2-13220	Bioengineering human stem cell-derived beta cell organoids to monitor cell health in real time to improve therapeutic outcomes in patients	**$1,198,550**	**N**	**80**	79	3	70	81	0	14	Y	N			
DISC2-13023	AI-aided rapid automated functional assessment for iPSC treatment of spinal cord injury	**$784,954**	**N**	**75**	74	4	60	80	0	15	N	Y			
DISC2-13120	GlyTR1-CAR T cells targeting abnormal N-glycans for the treatment of Glioblastoma	**$1,414,800**	**N**	**72**	73	2	70	75	0	14	N	N			
DISC2-13119	Development of Improved Stem Cells for Cardiac Cell-Based Therapy	**$1,410,267**	**N**	**70**	71	3	65	75	0	14	Y	N			
DISC2-13087	Treating acute respiratory distress syndrome by engineering phagocytic clearance of transplanted stem cells in the lungs	**$1,286,100**	**N**	**70**	70	11	50	92	1	13	N	N			
DISC2-13052	Autonomous System for Organoid Culture and Classification (ASOCC)	**$679,547**	**N**	**70**	70	5	60	80	0	12	N	Y			
DISC2-13015	Combating Ovarian Cancer Using Stem Cell-Engineered Off-The-Shelf CAR-iNKT Cells	**$1,404,000**	**N**	**70**	68	15	50	96	1	12	N	Y			
DISC2-13230	Development of a Stem Cell Fitness Biosensing Nano-bioreactor to Detect Accelerated, Pre-malignant and Malignant Stem Cell Aging	**$792,000**	**N**	**65**	67	3	65	75	0	13	N	Y			
DISC2-13026	Single-cell Assessment for Editing-associated Risk of Cancer for Clinical Use in Real-world Settings	**$806,412**	**N**	**65**	66	6	55	78	0	13	N	N			

APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Resubmission	Previous CIRM Funding	Disease Indication	Product Type	Approach
DISC2-13157	Investigate vision protection following injections of neural progenitor cells expressing GDNF at the middle stage of retinal degeneration	**$1,311,144**	**N**	**65**	66	2	65	72	0	13	N	Y			
DISC2-13154	Immune evasive CAR T cells	**$1,460,270**	**N**	**65**	65	1	60	65	0	13	N	N			
DISC2-13000	Quantitative & High Throughput Hematopoietic Stem Cell Purification	**$499,680**	**N**	-	-	-	-	-	0	12	Y	N			
DISC2-13194	Generating a transplantable synthetic kidney from human induced pluripotent stem cells	**$1,401,638**	**N**	-	-	-	-	-	0	15	N	N			
DISC2-13199	Development of a direct induction-based test for lithium response in mood disorders	**$649,975**	**N**	-	-	-	-	-	0	13	N	N			
DISC2-13100	Using diverse patient-specific hiPSC-derived lung organoids to identify the earliest lung cancer-initiating cells and events as potential drug targets	**$660,246**	**N**	-	-	-	-	-	0	15	N	Y			
DISC2-13125	The Pluripotent hESC-based Innovative Platform Enabling Regenerative Medicine Advanced Therapy for Amyotrophic Lateral Sclerosis	**$899,200**	**N**	-	-	-	-	-	0	13	N	N			

*** Qualify for Minority Report**

Application #	DISC2-13212
Title (as written by the applicant)	Preclinical development of an exhaustion-resistant CAR-T stem cell for cancer immunotherapy
Research Objective (as written by the applicant)	The expected outcome is an exhaustion-resistant CAR-T cell, which persists long-term in a functional progenitor T cell state in the tumor microenvironment and can be used for cancer immunotherapy.
Impact (as written by the applicant)	CAR-T cells are effective in B cell cancer, but less than 50% of patients experience long-term disease control. Exhaustion-resistant CARs may provide long-term benefit that extends to solid tumors.
Major Proposed Activities (as written by the applicant)	• Establish and optimize a CRISPR-engineered CAR-T stem cell therapy that resists T cell exhaustion. • Perform in vitro evaluation of TEx-resistant CAR-T cell tumor recognition and cytolysis, and progenitor cell state characterization, compared to conventional CAR-T cells. • Perform in vivo evaluation of TEx-resistant CAR-T cell function and persistence in xenograft tumor models, compared to conventional CAR-T cells. • Perform epigenomic characterization of T cell exhaustion in TEx-resistant CAR-T cell in tumor models, compared to conventional CAR-T cells.
Statement of Benefit to California (as written by the applicant)	A significant barrier to long-term efficacy of cancer immunotherapy is the development of T cell exhaustion, which limits T function in the tumor microenvironment. The proposed exhaustion-resistant CAR-T stem cell therapy candidate has the potential to benefit a large population of patients in California who suffer from a broad range of cancers that may be targeted by CAR-T cells, including solid tumors (lung, prostate, sarcoma, and skin) and blood cancers (leukemia, multiple myeloma, lymphoma).
Funds Requested	$1,420,200
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: 100

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	99
Median	100
Standard Deviation	3
Highest	100
Lowest	90
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 proposal have the necessary significance and potential for impact?
Yes: 13	• Sarcoma is a good target for immunotherapy. • This is an important topic and high potential for impact. • Improving the durability of CAR-T cell therapies for cancer is of great importance. • This project provides a new technology to address an important problem of CAR-T cell exhaustion for sarcoma treatment. • Technology with broad clinical applications.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• The premise of this application is that a major obstacle to durable CAR-T cell therapies is T cell exhaustion, and the applicants propose they have found a way to overcome this problem. • Prior work in the CAR-T field indicate that solid tumor microenvironment drives exhaustion of T cells. • The preliminary data motivating the technology is strong and provides a sound rationale. • Preliminary data is great.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 13	• Excellent revision, very responsive to the previous review. • The project is well-designed to end up with something that can be translated to the clinic. • The streamlining in response to the GWG comments provides a more realistic plan. • The focus on two targets increases the quality of the project. • Yes, the plan accounts now for a more comprehensive view of loss on T cell therapy persistence and function, in addition to exhaustion phenotypes. • The plan is appropriate.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 13	• The data are supportive of extending the T cell lifespan, and are based on careful studies on what the contributing factors are to T cell exhaustion. • The proposal is feasible, based on the preliminary data. • Very productive team with high likelihood of success. • The proposed team brings together experts in CAR-T. • The team seems to have access to all the necessary resources. • The budget is appropriate for the proposed work.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 12	• The investigators have accounted for the potential changes in the editing/manufacturing strategy due to race, ethnicity, sex and gender diversity. • Cancer affects all communities. • Yes, although there are no proactive efforts to reach out to the diverse CA population.
No: 1	*None*

Application #	DISC2-13051
Title (as written by the applicant)	Generating deeper and more durable BCMA CAR-T cell responses in Multiple Myeloma through non-viral knockin/knockout multiplexed genome engineering
Research Objective (as written by the applicant)	We will use integrated gene editing techniques to develop a new CAR-T cell therapy for multiple myeloma treatment
Impact (as written by the applicant)	Develop an improved CAR-T cell therapy for patients with refractory multiple myeloma and a new manufacturing strategy that circumvents the costs and inefficiencies of viral production.
Major Proposed Activities (as written by the applicant)	• Establish and optimize a CRISPR Cas9 editing strategy to generate combined non-viral TRAC-targeted BCMA CAR-T cells with RASA2 ablation. • Evaluate key functional characteristics of TRAC-targeted BMCA CAR-T cells with RASA2 ablation in vitro. • In vivo evaluation of RASA2 KO TRAC-targeted BCMA CAR-T cells in immunocompromised mice xenografted with multiple myeloma.
Statement of Benefit to California (as written by the applicant)	Multiple Myeloma (MM) is the second most common blood cancer, and currently there is no cure. The MM team at our institution, home to a multiple myeloma translational initiative, provides cutting edge care and offers hope through clinical trials to many Californians with refractory MM. We aim to develop an improved CAR-T cell therapy that will demonstrate deeper and more enduring MM responses in an early phase clinical trial here, and ultimately will become accessible to all patients.
Funds Requested	$1,463,368
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	3
Highest	94
Lowest	84
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	13
(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 proposal have the necessary significance and potential for impact?
Yes: 12	• The unmet medical need is to develop better treatments for patients with refractory/relapsed multiple myeloma (MM). They propose to do this by targeting therapies against the transmembrane glycoprotein BCMA, which shows expression largely restricted to normal and malignant plasma cells. • Current approaches for BCMA are only disease delaying with short durability. • Currently high response rates but low durability, so if this can improve durability, it will improve survival time. • The proposal will investigate a non-viral genetic engineering approach to generate chimeric antigen receptor T cells using state-of-the-art technology. • Site-specific integration of the CAR into the TRAC locus may enhance T cell functionality due to endogenous regulation of T cell activation. • RASA2-KO may enhance T cell activity against low antigen-expressing tumors and overcome immunosuppression. • The major benefits are to test the gene editing approaches. • It is unlikely that there will be any utility for additional BCMA targeting CAR-T products for myeloma given how crowded the field is. • As the underlying reasons are not known, it is not clear why the proposed approach would overcome current hurdles in BCMA.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 11	• The proposal is to generate novel CAR-T cell therapies for MM with enhanced persistence and therapeutic activity by targeting the CAR to the T cell receptor alpha chain locus. This is expected to improve product safety and uniformity, and has demonstrated enhanced CAR-T cell persistence in preclinical models. • There is also incorporation of RASA2 ablation in an attempt to enhance T cell function. RASA2 knockdown is a target that can boost T cell persistence to a wide spectrum of immunosuppressive factors. Ablation of RASA2 in preclinical models results in a longer period of tumor control. • Using CRISPR-Cas9 editing appears to be a viable approach to creating CAR insertions in the TRAC Locus. They can achieve high efficiency BCMA-CAR integration in the TRAC locus. • Preliminary data is sound, impressive, and supports the hypothesis that RASA2 TRAC-CAR T cells may show enhanced activity compared to current BCMA CAR T cells. • It is based on excellent preliminary data. • Non-viral approach is exciting and novel. • The problem is that the duration of response to BCMA-CAR T cell therapies is limited, with poor CAR-T persistence in patients. • Ultimately, it is not clear whether the issues being addressed are the major mechanisms for the long-term failure of BCMA CAR-T in MM.
No: 1	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 12	• Yes, approach is sound. The path to translation appears to be well thought out. • The strategy is very well designed. • It is appropriate to produce the product. • Will examine for chromosomal translocations through a method that was described well in the proposal. This is a concern for gene-edited cell products generated with 2+ double strand breaks. • Overall well designed, however, not clear why the applicants do not start with an FDA approved CAR.
No:	*none*

0	
GWG Votes	**Is the proposal feasible?**
Yes: 11	• All of the steps are logical and well thought out. • May quickly translate to phase 1 clinical trial. • Applicants are pioneers of the gene-editing technology and discovery of improved T cell functionality with RASA2 ablation. Highly feasible with this group. • The team is excellent. • The team consists of major contributors to this field. • The vast majority will be done commercially. • GMP reagents for ssDNA, Cas9, electroporation instrument. Six CAR designs will be investigated in this proposal so GMP virus is likely not available yet. • Is BCMA the right target? There are a number of current studies in this area and several competitors.
No: 1	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 12	• MM is currently not curable, even with current BCMA CAR T cells. African Americans have twice the risk for MM. Need for curative therapies is high. • Myeloma is increased in Black population. • Cancer is spread throughout all communities, and therapies will benefit all communities.
No: 0	*none*

Application #	DISC2-13020
Title (as written by the applicant)	Injectable, autologous iPSC-based therapy for spinal cord injury (SCI)
Research Objective (as written by the applicant)	We propose to develop and validate a therapy for spinal cord injuries in which human stem cell-derived neural cells are injected into the injured spinal cord using an injectable gel.
Impact (as written by the applicant)	Our study will address the critical need for an SCI treatment that significantly improves the neurological recovery and hence quality of life of SCI patients and their caretakers.
Major Proposed Activities (as written by the applicant)	• We will determine if delivering human iPSC-derived neural cells within our injectable gels will improve their ability to graft into and regenerate the injured spinal cord, as compared to saline. • We will evaluate if the differences observed in Milestone 1 are correlated with differences observed in the functional improvement of the different treatment groups. • Using multiple stem cell clones from the same donor as well as from distinct donors, we will evaluate what fraction of clones can pass multiple quality control criteria. • We will evaluate if distinct stem cell clones from different individuals can yield similar functional benefits when used to treat spinal cord injuries in rodents. • We will evaluate if different stem cell clones from the same individual can yield similar functional benefits when used to treat spinal cord injuries in rodents.
Statement of Benefit to California (as written by the applicant)	An estimated 17,900 cases of spinal cord injury are diagnosed in the United States annually, with an estimated lifetime cost of at least $1,217,266 per patient. As the state with the largest population number, California is most significantly affected by SCI. The success of our proposed research will significantly improve neurological and functional recovery in these patients, enhancing their quality of life, and reducing the economic and public health burden of the disease.
Funds Requested	$789,000
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All Grants Working Group (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	91
Lowest	89
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 proposal have the necessary significance and potential for impact?
Yes: 11	• Spinal cord injury (SCI) represents an important unmet medical need, with particularly high morbidity associated with chronic injury. • If the applicant is able to create viable new neurons and restore function in a model of chronic cervical SCI this would overcome significant bottlenecks in development of cell-based therapies for SCI. • The study is preclinical in nature and addresses an enormous unmet need. Improvement of quality of life and even partial restoration of function in SCI cases would have an enormous impact. • The applicant clearly defines the bottlenecks (variability in graft identity, variability in transplanted cell survival, variability in efficacy of a intraspinal transplantation of a fate-restricted population) and offers interesting solutions. • An additional strength is the focus on cervical SCI, which represents the majority of SCI cases. Over 80% of SCI models focus on lower segments. • CIRM previously funded the applicant's development of the injectable hydrogel to improve viability and function of iPSC-derived neural progenitors used in transplantations. The applicant completed all milestones and generated a total of 21 publications from the project. • The proposal addresses an important problem. • There is a great unmet need. • This is a solid project.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 11	• Transplanted iPSC-derived neural progenitors have been shown to stably integrate into the injured cervical cord, reduce inflammation, reduce cavitation and scarring, elicit robust regeneration of SCI-severed neural tracts, and restore sensorimotor function. However, long term synapse formation and long term neuronal survival are still a challenge and current approaches suffer from irreproducibility. • The scientific rationale is very sound with respect to the choice of neurons, the choice of injury, and the approach to providing protection for transplanted cells. In addition there are appropriate behavioral assays to evaluate efficacy. • The proposed use of a novel hydrogel cell delivery system that limits variability and improves survival of the graft is well rationalized through excellent preliminary data. • Strengths: Strong rationale, preliminary results, and potential for the development of a treatment for SCI. • Concern: The project per se does not test autologous transplantation; however, the testing of multiple iPSC lines is important for validation of the therapeutic candidate. • It would have been helpful if the applicant had expanded on future plans for the development of an autologous therapy. • Each aspect of the Project Plan is well thought out with respect to the path to translation. • The proposal includes good preliminary data showing durability of the treatment. • Preliminary data are very strong.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 11	• Overall, yes. The milestones are well constructed. The applicant plans to use a chronic (8 weeks post injury), hemisection, and contusion cervical SCI small animal model in

	combination with well defined iPSC-derived neurons and the applicant's encapsulation technology. • The preliminary data are quite striking. Using the applicant's encapsulation technology to deliver the nerve cells improved delivery, improved cell survival, enabled greater axonal extension, and was correlated with improved motor function. • Preliminary data could have been better explained - it is not entirely clear at what time post-injury the injection of cells occurred - the cited bioRxiv publication indicates use of a two weeks post-injury injection (corresponding to the early chronic phase). Are the preliminary data shown in the proposal from the same protocol, or are more delayed transplants shown? If the latter, the application would be even more exciting. • Why does the applicant propose to "jump" from transplanting two weeks post-injury to eight weeks? Is there a specific reason for this change in timing? Please explain. • Overall there is adequate discussion of pitfalls, except for in Milestone 1 where the solution for failed recovery is unclear and seems misguided. Why would using fibrogen or saline overcome a failed recovery in an eight weeks post-injury transplantation paradigm? Please explain the rationale. • There are some weaknesses in the discussion of future development of the product. Tests of transplantation at later (or earlier) time points could provide important insights. Also, the proposal does not include discussion of scaling, testing in larger animal models, regulatory hurdles, etc.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 11	• The objectives are straightforward and feasible: (1) Validate this transplantation therapy in a patient-relevant preclinical model. (2) Test the efficacy of a novel hydrogel cell delivery system against clinical standards. (3) Test the differentiation and therapeutic efficacy of transplantation of neurons derived from iPSC from multiple patients and clones to validate potential as an autologous therapy. • All of the milestones are logical and achievable, and the hydrogel is chemically defined and has been studied in the laboratory. • Strong research team with expertise in various fields that are relevant for the success of the application. • The applicant team shows great proficiency. • Productive team.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 11	• The proposal demonstrates awareness of diversity for clinical translation - while the Project Plan is not perfect representation of diversity, patient lines will be derived from non-Hispanic Blacks as they represent the largest growing minority demographic of SCI patients. • Cell lines are derived from people representing underserved communities. • The leadership and institution are committed to Diversity, Equity, and Inclusion values. • Spinal cord injury affects people across all boundaries.
No: 0	*none*

Application #	DISC2-13009
Title (as written by the applicant)	New noncoding RNA chemical entity for heart failure with preserved ejection fraction.
Research Objective (as written by the applicant)	Modified synthetic noncoding RNA molecule
Impact (as written by the applicant)	Heart failure with preserved ejection fraction
Major Proposed Activities (as written by the applicant)	• Lead optimization • Perform extensive preclinical testing and select a therapeutic candidate. • Develop and test preliminary potency assays based on mechanistic insights. • Demonstration of injury-modifying bioactivity in a clinically-relevant human progenitor cell population. • Optimize formulation and dosing for intravenous delivery, assessing biodistribution. • Optimize formulation and dosing for oral delivery. Plus Activity 7: Regulatory planning.
Statement of Benefit to California (as written by the applicant)	The target indication is heart failure with preserved ejection fraction (HFpEF), a highly lethal disease refractory to medical intervention. HFpEF is increasing in prevalence, and now accounts for most hospital admissions for heart failure in California. HFpEF disproportionately afflicts disadvantaged populations (women, Blacks and Latinos, and the elderly). Because the therapeutic candidate is universally applicable, the societal benefits of success here are expected to be profound.
Funds Requested	$1,397,412
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	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 proposal have the necessary significance and potential for impact?
Yes: 13	• The proposal focuses on HFpEF. This represents a disease of high prevalence and the current medical treatment options are very limited. The disease mechanisms underlying HFpEF are not well understood. The proposed mode of action of the identified drug adds novel insights into a potentially relevant disease mechanisms. The proposed mechanism is well-supported. • As HFpEF is currently a wide-spread and poorly treated heart condition, the use of this drug would meet an unmet need. • A new molecular therapeutic for heart failure with preserved ejection fraction would represent a significant advance with the potential to improve medical outcomes for a large patient population. • The proposal focuses on a distinct drug. This was identified as a component in extracellular vesicles derived from stem cell derived cells. This would qualify as a stem cell-derived product. By focusing on a distinct entity with an already established mode of action, there is a high likelihood of success. • The drug was originally identified via stem cell research, but the work has now moved past the stem cell research phase into a nucleic acid-based drug development phase. This grant is very translational in nature at present, and is focused on the optimization of a lead therapeutic. • The proposal is ambitious as it describes the progression from their current molecule to an oral or IV product. The process is well described, logical and has a high likelihood of success. • This grant focuses on the use of a drug implicated in heart failure with preserved ejection fraction (HFpEF). Use of this drug suppresses pathways including p21 and histone methyltransferases (HMTs) leading to heart fibrosis and heart failure. • Strong preliminary data using two complementary rodent models of heart failure suggest potential for the RNA-based therapy. • The project has a clear translational focus on lead compound optimization, delivery, and dosage. • A strong candidate with promise. • Lack of safety consideration at this point is a weakness.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• The overall rational is well described and developed. The proposed mode of action for the drug is well-described as it implicated and associated with established disease mechanisms relevant for HFpEF. • There is a strong premise for the drug to mediate paracrine-induced regeneration in the heart. Developing these compounds for treating heart failure patients is well-justified. • One major strength of the proposal is the extensive preliminary data. The drug is well characterized and the path from identification to characterization is well described. An additional strength is the fact that a modified drug has been developed which will serve as a starting point for the proposed experiments. • Strong preliminary data indicate the promise for the lead noncoding RNA to impact heart failure with preserved ejection fraction. • The preliminary data strongly supports a mode of action.

	• Yes, the proposal is based on preliminary data (which has been improved since the last submission) that outlines how a specfic YsRNA, found in exosomes secreted by cardiosphere cells has therapeutic effects on HFpEF, probably by inhibiting inflammation and ultimately fibrosis. • The applicants have made some considerable improvements in the elucidation of mechanisms, and now show that the lead candidate, suppresses two histone methyltransferases, which may then affect the regulation of p21. The drug may have the effect of reducing p21 leading to a suppression of fibrosis. • New data suggest a mechanism of action via suppressing histone methyltransferase activity. • Since the last review, the applicants have also improved the phenotyping of HFpEF in two mouse models. The detail and data concerning the macrophage experiments have been improved, and possible alternative sources cellular exosomes are now presented. • The availability of two disease relevant animal models and experience with the modules is a strength. • The drug was identified in stem cell derivatives. This could not have been accomplished differently. Therefore it is uniquely enabled by stem cells. • While the project has little direct relation to stem cells, the lead compound identification was enabled by studies demonstrating cardioprotective/regenerative activity in stem cell-derived cardiospheres.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 13	• The project, aims and milestones are very well developed and described in great detail. Each experiment and the progression to a potential therapeutic is well described and logical. • The research plan is essentially one of drug development of the present candidate. Since the drug has shown therapeutic value, the plan seems staged for translational development of this drug. • The project would first explore modified forms of the drug to improve stability and potency, then proceed to optimization of delivery and formulation, then proceed to planning for regulatory concerns and clinical trials. • The proposed experiments will address relevant questions which will generate important data towards a therapeutic. • The plan to improve stability of the drug is well-motivated. • The use of complementary models is a strength in that they potentially represent different heart failure patient populations. • In vitro investigation of the compounds on macrophage transcription in Objective 1 could provide insight into effects of the compounds. • Limitations and pitfalls are described and appropriate solutions are provided. • The timeline is ambitious. If successful, the proposal will contribute significantly to the mission of CIRM. • While new preliminary data on potential mechanisms are provided, the project will not directly investigate mechanism of action of the compounds. • The optimization of the drug will primarily occur in macrophage cultures. There is still some concern as to whether this is the ideal cell type in which to assess the drug derivatives, and whether results gleaned from macrophage assays will translate into efficacious approaches in vivo. This aspect—whether macrophage will also work in vivo (or not) is the source of some degree of risk to the project. • Macrophage assays are limited to transcriptional effects. Inclusion of phenotypic assays would strengthen the approach. • There is also a focus on using histone methyltransferase activity assays and epigenomic studies in the macrophages as a surrogate measure of efficacy. The utility of this approach is based on the notion that modulation of histone methyltransferase and epigenomic modifications are the primary mechanism of action. If other mechanisms of action (not tested) are important, then using the endpoints for drug optimization may not fully translate to efficacy in vivo (in the mouse heart failure models).

	• The use of histone methyltransferase activity and p21 activity as potency assays in Objective 2 is interesting and would be valuable. However, the plan to validate these compounds is unclear. • IV delivery of the compounds is well-designed. • There is some skepticism that oral or percutaneous delivery will really work, though alternate routes of administration are also possible. • Oral and percutaneous delivery is very high risk/high reward. While this may not work, the project has strong potential impact without it. • The project includes potential alternatives for investigation of activity in various model systems but lacks alternatives for compound design and delivery. • Delivery and safety aspects need further study. • There are some concerns about safety... will this drug induce proliferation or differentiation in other tissues? • Safety issues need to be tested.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 13	• The milestones are well described. There is a logical progression from further optimizing the drug, testing efficacy in a disease relevant cell model, and the evaluation towards a drug which can be administered to humans. • This project is logically designed, essentially based on a drug development and optimization pipeline approach. The research plan is essentially to first optimize the drug, then study its characteristics. An attempt to formulate an orally available drug will also be undertaken. • The proposal provides well-defined quantitative milestones. • The team is highly qualified to conduct the proposed experiments and studies. • The team is excellent, with strong experience in translating stem cell-based therapies to treat heart disease. • The resources are appropriate. • The budget is appropriate. • Lead compound optimization milestones are likely to be developed. Delivery milestones seem to have slightly higher risk. • Pitfalls and alternatives are presented for each aim, but these are not particularly well-developed.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	• Heart failure is a significant burden on all patient groups in California and elsewhere. Underserved racial/ethnic communities often have an even higher incidence of heart disease. The outcomes here would serve the needs of the diverse population in California. • HFpEF affects all races, ethnicities, sex and gender. In fact, minorities are at increased risk for HFpEF. • HFpEF is prevalent and a significant health burden especially in underserved communities. • Yes, the applicants make the case the HFpEF is prevalent in communities with disadvantaged economic resources and poor access to healthcare. • The proposed plan considers sex as a biological variable in experiment design. • Strong institutional commitment to DEI values and initiatives.
No: 0	*none*

Application #	DISC2-13232
Title (as written by the applicant)	Modulation of oral epithelium stem cells by RSpo1 for the prevention and treatment of oral mucositis
Research Objective (as written by the applicant)	Locally delivered formulation of RSpo1 protein as an activator of Lgr5+ epithelial stem cells in chemotherapy- or radiation therapy-induced oral mucositis
Impact (as written by the applicant)	Oral mucositis
Major Proposed Activities (as written by the applicant)	• RSpo1 formulation design and selection for optimal oral delivery • Activation of Wnt pathway by formulated RSpo1 in-vitro • Production of RSpo1 protein • Oral stem cell expansion by RSpo1 to protect and restore chemotherapy and radiation induced oral mucosa damage
Statement of Benefit to California (as written by the applicant)	The proposed research will provide a new therapy for the prevention and treatment of oral mucositis - a common complication of chemotherapy and radiation therapy for cancer patients in California, the US, and globally. If successful, the product development program will also enable growth of the institution which will bring more jobs and opportunities for California citizens, as the institution is based here.
Funds Requested	$942,050
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	88
Median	88
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 proposal have the necessary significance and potential for impact?
Yes: 13	• I think that in their resubmission, the authors have strengthened their proposal and answered all the critiques. The project has a high likelihood to result in a impactful product and meet the unmet clinical need to prevent the development of oral mucositis in cancer patients undergoing chemo- and radio-therapy. • This proposal has potential to be impactful. • New modality with a high and potentially broad clinical impact.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• Yes, Rspo proteins specifically co-activate Wnt signalling promoting proliferation of epithelial stem cells. In their previous publications they already demonstrated strong therapeutic potential of Rspo protein when administered systemically, however systemic administration carry risks of induction of inappropriate proliferation in other tissues sensitive for Wnt-signaling. To circumvent these risks authors propose to deliver the therapeutic locally in a mouthwash which will transform into the gel when in the mouth and cover mucosa thus maximizing retention. Applicants have experience with developing such formulations previously for applications into the colon. • Applicants will develop a specific and efficient potency assay to test the efficacy of their formulation in human cells. In addition they have established collaboration with the company to develop a large scale GMP-production of the recombinant Rspo protein. • In response to criticisms, authors have now included studies in human oral mucosa organoids and human gut organoids. • Functional efficacy of the mouthwash application in vivo will be tested in radiation- and chemotherapy-induced disease mouse models, where dose escalation studies will be conducted. Studies will be conducted to evaluate if restoration of the oral mucosa is mediated through expansion of the Lgr5 oral epithelial cells. Potential systemic toxicity will be also evaluated.
No: 1	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 13	• Yes, applicants have developed very clear plans for clinical translation. • Experimental plans are clear, logical and achievable, models are appropriate. Applicants will test Rspo formulations in primary human cells (organoid model derived from biopsies of gastrointestinal Lgr5 epithelial stem cells and in organoids derived from human mucosa) and in two relevant in vivo mouse models. • Need additional expertise with the human organoids. • The human organoid experiments do not seem very rigorous. Additional metrics and outcomes should be defined in advance of starting the studies.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 13	• The project is feasible, based on the exceptionally strong previously published and unpublished data, strong track record of the applicants in this area, all models are well established within the groups. • Organoids are not well-described.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	• Oral mucositis is a debilitating complication of chemotherapy and radiation therapy in all cancer patients, there is no clear evidence that its prevalence is related to race, ethnicity, sex, and gender identity. • The attention to underserved communities is weak.

	• There is an expression of support for DEI values, but the description is not very thorough or robust.
No: 0	*none*

Application #	DISC2-13077
Title (as written by the applicant)	Transplantation of genetically corrected iPSC-microglia for the treatment of Sanfilippo Syndrome
Research Objective (as written by the applicant)	This research will discover whether transplantation of stem cell-derived microglia can be used to treat Sanfilippo Syndrome, a devastating and currently untreatable childhood neurological disease.
Impact (as written by the applicant)	If successful, this research will identify a promising new therapeutic approach for Sanfilippo Syndrome and provide the first evidence that stem cell derived microglia could be used therapeutically.
Major Proposed Activities (as written by the applicant)	• We will use CRISPR technology to correct disease-associated mutations in the sulphoglucosamine sulplhohydrolase (SGSH) gene in human stem cell lines that we have generated from patients with Sanfilippo Syndrome (SS). • Patient-derived and CRISPR corrected stem cells will be differentiated into microglia, an immune cell type that is dysfunctional in SS, and then transplanted into a small animal model of this disease. • Three months after transplantation we will examine SS-associated neuropathologies to determine whether transplantation of genetically-corrected microglia has reduced disease pathology. • Microglia that are engineered to produce and secrete higher levels of the missing SGSH enzyme may provide additional long term benefits. We will therefore test the efficacy of this additional approach. • Six-months after transplantation we will examine neuropathologies to determine whether SGSH secreting microglia improve cognitive function and provide additional long-term benefits in SS small animal models. • Analysis of biomarkers, neuropathology, cognitive function, and RNA sequencing of brain cells will be used to determine the optimal approach to reduce SS cognitive deficits and neuropathology.
Statement of Benefit to California (as written by the applicant)	Sanfilippo syndrome (SS) is a devastating pediatric neurological disease that effects families of all ethnicities and race including many Californians. Sadly, currently approved therapies provide little benefit. Our research aims to develop a new stem cell-based therapy for SS that uses microglia, the immune cell of the brain. If successful, this new approach could also potentially be developed to treat many other neurological diseases that are highly prevalent in California.
Funds Requested	$1,199,922
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All Grants Working Group (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	86
Median	87
Standard Deviation	2
Highest	88

Lowest	83
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 proposal have the necessary significance and potential for impact?
Yes: 11	• San Filippo Syndrome (SS) is a genetic lysosomal storage disorder that causes neurodegeneration and decreased life expectancy. The defective gene in SS is SGSH, a sulphoglucosamine sulplhohydrolase. This proposal seeks to determine if human induced Pluripotent Stem Cells (iPSC) derived from SS fibroblasts, combined with CRISPR correction of the genetic defect, followed by differentiation to microglia, and finally transplantation into a small animal model, can correct a mouse model of this disease. • SS is currently treated only palliatively and this approach might result in a cure. A previous gene therapy trial to restore SGSH was halted, to an ex-vivo stem cell gene correction combined with transplantation might be successful. • The proposed technology could have a large impact on the treatment of SS, by providing IPSC-derived microglia able to supply the missing enzyme needed in order to digest heparin sulfate glycosaminoglycans (GAG). • Due to the ability to derive microglia from the patient's own cells, the proposed approach could provide a significant enabling technology for the treatment of a host of currently untreatable diseases. • This proposal describes a strong candidate involving both stem cells and gene editing. • The rationale for targeting microglia and the disease-causative gene is understood but the rationale for using human microglia for the entirety of the preclinical study is less clear. While it is relevant to test human microglia to ensure they are not toxic, efficacy would be best addressed through the incorporation of microglia from the small animal model. • It is very possible that human microglia have a beneficial effect in a small animal model brain simply because they are human microglia. Repeating the study with mouse microglia would address this problem and provide stronger data that the correction of the gene within microglia is truly responsible for the beneficial outcomes. • The preliminary data strongly support the use of microglia as the cells for engraftment, in particular in light of the fact that microglia express high SGSH protein levels (Figure 1). • Data also show that conditional deletion of SGSH in several brain cell types (e.g. neurons, astrocytes, endothelial cells) does not recapitulate the pathological accumulation of heparan sulfate (Figure 2), suggesting that these other cell types may not be the most important cells in the pathology. However, to make a stronger argument, it would be necessary to show the effects of conditional deletion in microglia on heparan sulfate accumulation. • The presented data further demonstrate that the team has already established the proposed SGSH knockout small animal model and has begun biochemical characterization. • Although not shown in this proposal, the group has already published on a transplantation paradigm to deliver iPSC-microglia into the forebrain of postnatal SS animals. • The preliminary data provides both scientific evidence to support the rationale as well as a clear indication that the team is capable of performing the proposed study.
No: 0	*none*
GWG Votes	**Is the rationale sound?**

Yes: 11	• This proposal falls within CIRM's scope. The project plan requires the use of human iPSC, their genetic correction, and transplantation of their differentiated derivative cells. Thus this is a stem cell grant uniquely enabled by iPS approaches. The grant also incorporates gene correction approaches, also of interest to CIRM; these will be performed in iPSC themselves prior to differentiation and engraftment. • While one can understand the reasons the applicants opted to use human microglia, this decision has several disadvantages, such as the requirement to use humanized and immunodeficient animals to prevent cell rejection as well as the possibility that the human microglia contribute to any potential improvements. • The rationale is sound. Microglia are able to migrate throughout the brain, and they are able to digest materials that need to be eliminated. It is probably the best candidate cell type for trying to treat a disease of this nature. • Loss of the SGSH gene (expressed most highly in microglia) results in failure to degrade glycosaminoglycans (GAG), which accumulate pathologically in microglia. This approach would add back cells, via stereotactic injection into the brain, hopefully restoring SGSH function and alleviation of SS pathology. • This group (using CIRM funding) was able to produce microglia readily and reliably from human iPSC (published in Neuron). As microglia can migrate, these became 80% of microglia in xenografted mouse brain. • One major concern for this study is that the experiments in the mouse model may not adequately replicate what will be performed in patients. • Microglia are an interesting target for multiple diseases.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 9	• Yes - a candidate stem cell therapy approach to treat SS may be ready for large animal and eventually human translational research at the conclusion of this small animal model research. Ultimately, iPSC would need to be derived from patients, CRISPR-edited to restore SGSH function, then differentiated to microglia and injected into the brain to achieve a therapeutic outcome. • It is a well constructed project that will greatly advance our understanding of how to use glial cells to mitigate neurodegenerative diseases. It is a novel approach in the field of cell replacement therapy that could benefit other diseases. • At the end of this research, if successful, the outcome will be the cure of a mouse model with a stem cell therapy. Considerable translational research will be needed to take this to humans. Overall, it is the approach, rather than cell lines, that will be of value, as the ultimate treatment would start with creating patient-specific iPSC. • Though the project plan contains 11 milestones, these fall under two specific aims. 1: Can CRISPR-edited microglia (of iPS origin) alleviate the small animal SS-like pathology, and 2: is there value in creating microglia that over-express SGSH, as it might be more therapeutic to use super-expressor cells to clear accumulated glycans. • Yes. The project plan and milestones are logical. Milestone 1: CRISPR correction of SGSH in patient derived iPSC, 2: mouse breeding of an existing SGSH model, 3: xenografting , and 4: xenografting with SGSH overexpressing cells, 5: analysis of engrafted microglia, 6: measurement of lysosomal storage, 7-11: cognitive assessments in engrafted animals and other characterization. • A pitfall and alternatives paragraph for Milestone 1 is present, but basically says that no problems are likely. Milestone 2 seems to lack such a section completely. • The applicant already has generated and validated the required small animal model. They also have developed means of genetically modifying microglia. • The process appears to be scalable. The safety appears to be very good. • One weakness is that they have no proof of principle for in vivo treatment yet. • Another weakness is that there is no attention to the question, which is well recognized in the lysosomal storage disorder field, as to whether the missing enzyme is secreted and can be taken up by other cell types. This will be very important in the analyses. • Related to this point is the problem with accumulation of GAG in the extracellular space. If so, then microglia may be sufficient. If the problem involves GAG messing up lysosomal function in multiple cell types, then secretion and uptake of enzyme are critical issues.

	• There are also concerns about insufficient cell lines, and insufficient powering of the studies. • A strength of the project is the use of multiple readouts of therapeutic benefits, i.e. protein aggregation, neuroinflammation, SGSH protein levels etc. It is unclear, however, why applicants propose to measure phospho-tau levels. • Cell-autonomous and non-cell-autonomous effects should be thoroughly considered. • The sample size for the biochemical and microglia portions of the animal study seems underpowered. A sample size of six for biochemistry is the bare minimum required to see strong effects. Additional animals would increase the power of the study. • For the behavioral studies, the applicants indicate that the elevated plus maze is a cognitive task. This is incorrect. The elevated plus maze measures anxiety-like behavior and has been validated as a correlate of cortisol levels. If the applicants intend to perform anxiety testing, this should be stated and justified.
No: 2	*none*
GWG Votes	**Is the proposal feasible?**

Yes:
11
	• Yes - this is a talented stem cell and microglia team with support from an appropriate SS small animal model team. The milestones are logical and achievable in the two year timeframe, though this will be a somewhat compressed timeframe should difficulties be encountered.
	• The Principal Investigator and co-investigators are proficient in iPS derivation, engineering, and differentiation to microglia. Collaborators include the researchers who made the SGSH knockout mouse model.
	• The applicants only superficially address potential pitfalls and alternative strategies. A number of questions arise when reading the proposal:
	  • The brains of the small model animals display astrocytosis, microgliosis and synaptic alterations. It is likely that iPSC-derived microglia may alter their phenotype in response to this pro-inflammatory environment. Can this affect the therapeutic benefits of engrafting microglia?
	  • In Milestone 2, the investigators propose to measure neuronal loss. Neuronal loss occurs at 7-8 months of age but according to their timeline, they will not wait 7-8 months to assess this variable.
	  • The experimental design will use one male and one female iPSC line. Given the variability of patient-derived iPSC and the intrinsic variability in the biology of male versus female microglia, the use of a single iPSC line per gender is questionable.
	  • Milestones are reasonable, however the timing for certain milestones could be better planned. For example, the applicants intend to wait until they have successfully injected mice prior to developing overexpressing iPSC-lines. These two lines of research could be more efficiently completed if they occurred concurrently.
	• This group has pioneered microglial generation and their genetic modification, and clearly can do this.
	• The project can be completed in the proposed timeline. The team has a strong expertise in all aspects of the grant, from iPSC culture to CRISPR gene editing and in vivo studies.
	• The team has already begun validating the small animal model and expanding their colony. They are experts in differentiating iPSC into microglia.

No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 11	• The project plan and design includes the use of both male and female mice as well as stem cells so this is adequately addressed. Ethnicity is not currently taken into account but this is due to problems with availability. The applicants are taking steps to rectify the situation. • The incidence of SS is elevated in Eastern European populations, but also occurs throughout all ethnicities. In addition, there may be sex-based differences. These are

	discussed and included in the research plan, especially in the use of both male and female iPSC lines. ● The team has shown a strong commitment to Diversity, Equity and Inclusion values. ● Little in the proposal is specific to underserved populations, perhaps due to the type of research being proposed. ● Diseases like this do not discriminate between populations.
No: 0	*none*

Application #	DISC2-13201
Title (as written by the applicant)	Matrix Assisted Cell Transplantation of Promyogenic Fibroadipogenic Progenitor (FAP) Stem Cells
Research Objective (as written by the applicant)	We seek to develop a cell-based hydrogel therapy to improve outcomes in patients with muscle degeneration. The technology will improve muscle through sustained release of cell-based cytokines.
Impact (as written by the applicant)	While designed for rotator cuff injuries based on the model, low back pain and spinal degeneration as well as traumatic muscle loss would be well served by this therapeutic.
Major Proposed Activities (as written by the applicant)	• Evaluation of pro-myogenic activity of human FAP in co-culture experiments. We will confirm the ability to isolate human FAP and differentiate into a pro-myogenic subpopulation of myogenic FAP. • Optimization of hydrogels for engrafting of FAP. We will select one candidate HyA hydrogel formulation that allows for the highest pro-myogenic and beige fat gene expression of implanted FAP. • Characterization of hydrogel-FAP transplantation in a delayed rotator cuff repair. We will implant hydogels plus FAP in a delayed rotator cuff repair model to determine effects on muscle quality.
Statement of Benefit to California (as written by the applicant)	The proposed research will be of significant impact to the citizens of California. Given the aging population, an increasing number of California citizens are likely to develop rotator cuff injuries and other conditions that result in muscle degeneration. If successful, this product would offer the first treatment to treat localized muscle atrophy and degeneration through a cell based transplant strategy that stimulates exogenous and endogenous delivery of promyogenic factors.
Funds Requested	$1,179,478
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All Grants Working Group (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	85
Median	87
Standard Deviation	3
Highest	87
Lowest	75
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	11
(1-84): Not recommended for funding	2

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 proposal have the necessary significance and potential for impact?
Yes: 13	• Treatment strategies to improve muscle quality after rotator cuff tears and associated secondary muscle degeneration including atrophy and fatty infiltration (FI) are critical to improved surgical outcomes and would directly translate to other muscle injury processes such as spine degeneration, aging, and cancer cachexia. • The therapeutic is aimed at providing promyogenic activity where there is muscle degeneration, fatty infiltration, and a need for surgical repair. Torn rotator cuff (with an incidence of 250 thousand cases per year) is the most obvious clinical target. Spinal fusion surgery (300 thousand procedures per year) may also be a target. • The proposal addresses a clear clinical indication. Approximately 62,000 torn rotator cuff patients have visible fatty infiltration and would be candidates for this muscle transplantation procedure. • Fibroadipogenic progenitors (FAP) are responsible for fatty infiltration after rotator cuff tears and can differentiate into a beige adipose tissue (BAT) phenotype that may have a role in promoting muscle recovery and regeneration. The unmet need is among patients with large rotator cuff tears, where native FAP lack the capability to differentiate into promyogenic FAP-BAT. Thus, muscle in large tears does not regenerate successfully, and transplantation strategies for functional FAP-BAT are needed. • Translation to the clinic is minimally discussed.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• The rationale is sound. The original version of this application lacked careful justification of the complex hydrogel, as well as clarity on whether to use an autologous versus allogeneic transplantation. However both these weaknesses have been very well addressed. It is now clear that the complex scaffold will add value and that the clinical plan is autologous therapy using a patient biopsy from a healthy, unaffected muscle. • The applicant was the first to demonstrate the effects of key cross-linkers with different sensitivities on HyA hydrogel function in vitro and in vivo; protein expression and retention were significant for the slowest degrading cross-linker; and cell survival was highest in their matrices in conjunction with slow degradation of the transplant and rapid vascularization. • The rationale is sound but the experimental plan is not properly designed to address the main hypothesis behind this project.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 11	• The work plan is broadly logical. Milestone 1 is useful though not a significant advance; nonetheless it will provide good data for future regulatory purposes. Milestone 2 is fine-tuning of the scaffold and will be essential for delivery of the therapeutic, although it will not address the key question of how to balance complexity with clinical gain. Milestone 3 is a pivotal study, assessing the efficacy of the applicant's transplantation procedure in rescuing gait in a mouse model of injury. Milestone 3 is now supported by the applicant's published work demonstrating that transplantation of FAP-BAT improves muscle quality in the mouse model. In addition, new data (Figure 9) show that delivering FAP in HyA hydrogel is effective at promoting promyogenic gene expression and vascularization among transplanted cells. • The applicants process for FAP-BAT cell isolation and purification is now supported by preliminary data (Figure 7). Key preliminary data indicates undifferentiated FAP increase muscle protein expression when cultured in the applicant's hydrogel (Figure 8). In this proposal they will work out peptide concentrations. • I have no major concerns with this work plan. • The proposal has been revised to address previous concerns.

	• Feasibility has been demonstrated for most milestones. • Potential pitfalls and alternative approaches are discussed. • The proposal includes appropriate timelines to demonstrate proof of concept in a mouse model.

No:
2
	• The in vitro work is difficult to interpret, as clinical translation is never guaranteed.
	  • The premise of BAT inducing regeneration is supported by the literature, but there is no evidence these pharmacologically induced cells will exhibit the same function.
	  • Satellite cells and FAP will be isolated from healthy muscle. BAT will be induced from FAP, and then co-cultured with satellite cells. In a clinical setting, how will the satellite cells be maintained prior to this?

GWG Votes	**Is the proposal feasible?**
Yes: 13	• Overall, the milestones are clear and achievable. However, success criteria for Milestones 1 and 2 are poorly described. Evaluation of gene and protein expression in satellite cells following co-culture with FAP alone and FAP-BAT is descriptive and not quantitative. • The multidisciplinary team includes an expert in orthopedics (the PI) plus an expert in biomaterials. • The team is solid and has the needed resources. • The project is feasible. The PI and collaborator have the expertise to conduct the proposed project. • The work is feasible and can be undertaken as planned - I have no major concerns. • Excellent resources and environment. • Appropriate budget.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	• The applicant discusses potential benefits of treatments to patients with lower socioeconomic status, as well as plans to sample from diverse donors. • Cells from diverse communities will be utilized. • Sampling from a diverse population is described.
No: 0	*none*

Application #	DISC2-13063
Title (as written by the applicant)	Improving the efficacy and tolerability of clinically validated remyelination-inducing molecules using developable combinations of approved drugs
Research Objective (as written by the applicant)	The candidate is a fixed dose binary small molecule drug combination, consisting of two agents that act synergistically on a multipotent stem cell population in the CNS to stimulate remyelination.
Impact (as written by the applicant)	The proposed studies will address bottleneck issues related to the effect size and tolerability of clinically validated remyelination drug classes.
Major Proposed Activities (as written by the applicant)	• Establish the maximal and minimal effective concentrations (ECmin and ECmax) and associated levels of efficacy for defined combination-based drug therapies in three populations of rat oligodendrocyte progenitor cells (OPCs). • Establish maximal and minimal effective concentrations and associated levels of efficacy for defined drug combinations in a population of human OPCs. • Demonstrate reproducible disease modifying activity (i.e., enhancement of remyelination efficiency) in vivo using the cuprizone model of demyelination/remyelination. • Complete mouse brain pharmacokinetic (PK), drug-drug interaction and preliminary rodent tolerability studies for 3 OPC differentiation-inducing drug combinations. • Complete mechanism of action studies • Complete penultimate in vivo efficacy study with kinetic measures and imaging outputs using the cuprizone model of demyelination/remyelination.
Statement of Benefit to California (as written by the applicant)	It is estimated that >120,000 California residents suffer from multiple sclerosis (MS). This proposed research aims to provide a disease modifying therapy for MS. It will have a significant beneficial impact, by targeting the regenerative process known as remyelination, which becomes limiting during the progressive phases of MS disease.
Funds Requested	$1,554,126
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	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 proposal have the necessary significance and potential for impact?
Yes: 13	• Yes, a disease modifying drug for multiple sclerosis (MS) would impact an unmet need. The outcome of this work will be the identification of a highly efficacious fixed dose drug combination remyelination therapy. Because both agents will be FDA approved drugs, translation to the clinical will be accelerated. • The product is designed to represent a fixed dose binary small molecule drug combination formulated for oral delivery in patients with relapsing-remitting multiple sclerosis (RRMS). • Both drugs are individually FDA approved, penetrate the blood brain barrier and act on an adult stem cell population in the CNS to stimulate the process of remyelination. The drug can be used alone or in combination with standard of care immunomodulatory agents. • The project uses FDA-approved drugs, which should accelerate translation of the findings to the clinic. • Great chance to get into the clinic. • Combining these two drugs is logical. • The proposed therapy would increase the differentiation of oligodendrocyte progenitor cells (OPCs) into functioning oligodendrocytes, thus leveraging a physiological regenerative process. • The applicants have a patent on a class of OPC differentiation-inducing drugs. • The proposed drugs will be tested for tolerability and drug-drug interactions in vivo. • The applicant has not explained how the data from this grant will be leveraged to advance the therapy to a clinical trial.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• The drugs were found to induce a statistically significant positive impact on remyelination and were identified using the discovery platform described in this proposal. However, the magnitude of observed effects and dose limiting toxicity likely limit further development of either of these agents as monotherapies. The applicant thus proposes a combination therapy. • Yes, synergistic combinations of two drugs can work better than either drug alone. • Yes, the proposed strategy of using a combination drug therapy has the potential to improve and potentiate remyelination in patients with Multiple Sclerosis (MS) and relapsing-remitting MS patients. • Good rationale. • The rationale for the drug choice/development is based on previous clinical trials that have met primary endpoints or that have come very close to it. Improving on these drugs, either alone or in combination is therefore a relevant approach that is also likely to yield rapid translatable therapies for patients. However, insufficient data was provided to explain the rationale for testing the different drug combinations.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 13	• Sound methods and ideas. This appears to have a good chance of success. • Applicants completed pairwise combination drug screens that resulted in the identification of two unique pairs of mechanism classes, involving a clinically validated partner, which when combined have a significant impact on overall efficacy. • Based on preliminary data they want to demonstrate enhancement of remyelination efficiency in vivo, demonstrate reproducible activity in a human OPC population, generate

	mechanism of action data by validating putative targets, complete brain pharmacokinetic studies and generate preliminary safety and tolerability data for defined small molecule drug combinations. ● The plan is straightforward. ● The preliminary data is not well explained and thus difficult to understand. Very little preliminary data was provided in relation to the specific class combinations. The in vitro data is difficult to read or limited to western blot analysis. The preliminary data section referenced, in large part, ongoing clinical trials which only partially justified the study rationale.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 13	● The group has already started with experiments to significantly improving remyelination efficiency at well tolerated dosages of approved drugs, and has completed two major CIRM funded activities. ● The team is highly qualified - proposal builds upon multiple years of preclinical work from this laboratory, which has led to two recently completed phase 2 clinical trials in relapsing-remitting MS patients. ● Seems highly ambitious but they did similar studies before; strong preliminary data. ● The proposed experiments and rationale are, for the most part, well-constructed and likely to result in information that can improve treatment for MS patients. However, the overall combination of experiments is confusing and rather poorly organized. ● Potential pitfalls and alternatives are not systematically addressed. In particular, the mechanistic aspect of the grant is not well detailed and the pitfalls not identified. This aspect is particularly concerning because, in contrary to other aspects of the grant, the investigators do not provide preliminary data suggesting that methods are in place, nor working as expected. ● The timeline shows that mechanistic, in vivo and rodent cell-based profiling will all begin at the same time. One could ask if in vivo and mechanistic experiments should come after cell-based profiling.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	● Institutional commitment to DEI values is clear. ● Diverse underserved communities will benefit should the translational efforts be successful. ● All MS patients would benefit, though the cost of the drug is not addressed. ● The project aims to serves all communities. However, the investigators did not address if there are known barriers that prevent subsets of MS patients to access available therapies and how they would address those.
No: 0	*none*

Application #	DISC2-13213
Title (as written by the applicant)	Extending Immune-Evasive Human Islet-Like Organoids Survival and Function as a Cure for Type 1 Diabetes
Research Objective (as written by the applicant)	Determine optimal islet transplant conditions and systemic treatments that promote graft survival upon transplantation into immune-competent diabetic subjects.
Impact (as written by the applicant)	Our proposal will optimize the generation and viability of an unlimited, reproducible source of human engineered islets for transplantation.
Major Proposed Activities (as written by the applicant)	• Demonstrate improved organoid graft survival with FGF1 coating • Prolong grafted organoid survival by reducing metabolic insulin demand
Statement of Benefit to California (as written by the applicant)	Diabetes affects 3 million people in California. Type 1 diabetes is a particular burden as it requires life-long administration of insulin. Allo-transplantation of islets is limited by availability of donor cells. This proposal will facilitate the generation of functional ESC-derived islet-like organoids as an unlimited, reproducible source and optimize methods to increase functionality and viability upon transplantation into diabetic patients.
Funds Requested	$1,523,285
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	88
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 proposal have the necessary significance and potential for impact?
Yes: 12	• High unmet need and replacement therapy is necessary to alter the course of Type 1 Diabetes (T1D). • Improving organoid engraftment and survival would provide a potential new cell-based therapy for T1D. • A two-pronged approach of improving vascularization and reducing metabolic stress is an advantage of the approach. • The project represents early stage translational efforts in a mouse T1D model, which is appropriate. • Subsequent translational efforts are not described but presumably the team would transition to larger animal models in their translational program. • High risk and high reward project.
No: 0	• Having the applicant group turn their attention to beta cell biology and the problem of diabetes is most welcome. The paper last year from the group is of considerable interest for the effects of a protein on maturation of human islet-like organoids. In addition, a homozygous knock-in in these cells was made and it was shown that these cells could survive and function when transplanted into STZ diabetic mice. This is a revised proposal which is considerably improved. • This is a resubmission of an application that had some attractive components but there were concerns about the feasibility of some of the proposed experiments. • As described in the introduction the revision is better focused. The plan to use a peptide combined with FGF1 to target beta cells has been abandoned and the focus on FGF1 has been sharpened. They now emphasize that they expect the affinity of FGF1 for heparin sulfate proteoglycans will be sufficient to provide good coating of the organoids, but they may need a backup approach of making FGF1 bound beads. More details have been provided about the tissue clearing technology, an attractive approach. • Concerns were raised about the use of the kidney subcapsular space for testing the effects of FGF1, but better justification has been provided. Indeed, the kidney site has proved very useful for obtaining information that is useful when moving to more clinically applicable sites, such as liver or omentum, although interest in using an adipose tissue site was expressed. • In the earlier proposal, there were concerns about whether the blood glucose levels were not truly normalized because they often hovered in the range of 300 mg/dl, rather than falling to the normal level in mice, which is below 200 mg/dl. In the revision, they explained that submaximal numbers of organoids were purposefully used, although the rationale for this was not fully explained. The data of the revised application does not eliminate this concern. • In Figure 1 of the revised application, the transplanted organoids again failed to truly normalize the glucose levels. With human islets and beta-like cells generated from stem cells, the expectation is that glucose levels will be maintained below 200 mg//dl. Applicants suggest that increasing the dose will solve this issue. • The present proposal is focused on the possibility that FGF1 can be used to improve the effects of transplanted organoids. Data are presented showing that FGF1 can lower blood glucose levels by inhibiting hepatic gluconeogenesis through mechanisms that are separate from insulin. In addition to FGF1 effects to lower glucose levels, FGF1 could also be used to enhance the vascularization. • Success depends on whether the current proposed experiments support the concept.
GWG Votes	**Is the rationale sound?**
Yes: 12	• The premise of using FGF1 to increase vascularization and reduce metabolic stress is sound. FGF1 is a known proangiogenic factor and this team has done significant work to demonstrate FGF1 regulates glucose homeostasis and suppresses adipose lipolysis in HILOs. • The team presents strong preliminary data demonstrating mature phenotypes and immune suppression in HILOs. • Compelling preliminary data demonstrate metabolic effects of FGF1 in HILOs • The ideas are novel and worth pursuing. The plan is to use stem cells. • Good preliminary data.

	• The preliminary data are not extensive. Questions can be raised about whether FGF1 will be effective in reducing that loss of islet tissue the occurs during the first 3-4 days after transplantation. • There is little preliminary data indicating pro-angiogenic effects of FGF1 in the organoids.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 12	• The project is clearly focused on two complementary goals, increasing vascularization and reducing metabolic stress. Aims are carefully designed with the translational focus of improving organoid engraftment and survival. • The experimental plan is good science proposed by a top investigator. • Assessment of organoid functionality in vivo is strong. • Yes. Milestone 1: Establish transplant conditions that maximize grafted organoid survival. There are high expectations that enhancement of the vascularity of transplanted cells will lead to major improvements of outcome, but this may be overly optimistic. Beta cells normally promote vascularization by secreting VEGF and no doubt other factors, so it is not clear how much more can be achieved, particularly during the first two days after transplantation when death from hypoxia is likely maximal. • The techniques that are proposed to evaluate the transplants are elaborate and well described – these being tissue clearing, formation of vascular networks, and evaluation of inflammation using panels to measure cytokines. These techniques will provide good information about what is going on with the transplanted cells, but the major issue is whether providing local FGF1 will be beneficial at all and if so, at what times. • The FGF1 coating process in objective 1 is simple, but doesn't offer much control over dosing or release (this is addressed in part in the pitfalls and alternatives). • Imaging-based measures of organoid vascularization are clearly-described. However, it isn't clear whether the vascularization will come from the mouse or human cells. • There was a suggestion that the organoids might do better if transplanted into white or brown adipose tissue, but a rationale for this suggestion was not provided. • A weakness with this section continues to be the relative lack of preliminary data. It is hard to imagine that addition of FGF1 or any other combination of factors will be able to prevent the critical loss of cells that will occur during the first few days, but it is entirely possible that important later effects will be seen. • Milestone 2: Demonstrate extended organoid graft survival by reducing metabolic insulin demand. The plan is to use subcutaneous injections of FGF1 to complement the coated organoids. There is a good plan to evaluate the transplanted cells with a clearing technique. There is also a plan to perform RNA velocity and pseudo time trajectory on scRNA-seq data, although the value of doing these analyses is not made clear. Also mentioned were some plans to evaluate ER stress, which were not well-developed. • Single cell transcriptomics analysis of organoids in aim 2 is clearly described and is a good way to assess the effects of FGF1 on different cell populations through time. • Measures of metabolism in aim 2 are indirect, relying on transcriptomics. • There are two major issues with these plans to evaluate the interventions. The first is whether promoting vascularization will have a major effect on survival. It is hard to be optimistic about this. The second issue is the immune response to these organoids. The proposed detailed analysis of the transplants could provide important information about immunological events, which could be used to improve outcomes. • Could have done a better job with pitfalls.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 12	• The risk of the project is appropriately balanced by high potential reward. Success in improving organoid viability seems likely. • The team is a strength of the project. They are at the forefront of developing cell therapies to treat T1D. • Outstanding scientist working in one of our top institutions. • This is a good team.

	• Milestones are clear and quantitative.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 12	• T1D poses a major health care challenge across society and exerts a particular burden on underserved communities. Improved cell therapies for T1D would impact quality of life and potentially reduce health care costs across the diversity of California's population. • Yes, but of course T1D is less common in underserved communities. • The team clearly described diversity and inclusion in the research team. • Sex as a biological variable is not considered in research design.
No: 0	*none*

Application #	DISC2-13136
Title (as written by the applicant)	Meniscal Repair and Regeneration
Research Objective (as written by the applicant)	Stem cells are seeded into fibers spun out of collagen to fabricate tissue that resembles the knee meniscus
Impact (as written by the applicant)	Meniscal tears are very common but do not heal. The treatment is removal of the torn tissue, which leads to osteoarthritis. If successful, replacing the tissue will prevent osteoarthritis.
Major Proposed Activities (as written by the applicant)	• Establish the identity and purity of the stem cells • Show proof of tissue regeneration in laboratory experiments • Show proof of meniscus regeneration in live animals • Conduct INTERACT meeting with the Food and Drug Administration (FDA) to discuss the preclinical studies needed before clinical trials
Statement of Benefit to California (as written by the applicant)	Annually, over 100,000 Californians sustain meniscal injuries, the majority of which result in surgery for removal of damaged tissue. These injuries accelerate the early development of osteoarthritis, for which there is no effective treatment other than total joint replacement, which is a major operation. There are significant socioeconomic benefits to preventing disabling osteoarthritis. The reductions in healthcare costs are also likely to be significant.
Funds Requested	$1,620,645
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All Grants Working Group (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	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 proposal have the necessary significance and potential for impact?
Yes: 12	• Meniscal tears are common and no effective treatment options exist. The proposal uses a combination of stem cells and a scaffold to replace allografts or other types of cell free scaffolds. If the product produces meniscal cartilage without calcification or other unwanted cell types it would be an important advance. • Yes. The annual incidence of meniscal injuries in the US is ~750,000 with 90% resulting in meniscal surgery. Although not usually life threatening, these injuries are a major health burden. Allografts and artificial menisci have limitations, so the proposal is to a create biomimetic scaffold seeded with differentiated meniscal progenitors that proliferate locally and secrete matrix components that integrate into the scaffold. • Meniscal tear is a common injury for which there is no adequate treatment except for the minority of cases where the tear is in the vascularised outer third of the meniscus. For the majority of tears, in the unvascularized, white zone, the standard of care is partial meniscectomy. This removal of the damaged tissue produces good short-term outcomes but poor long-term outcomes, with the frequent development of osteoarthritis. • The proposed technology will attempt to replace the meniscal tissue removed at meniscectomy, using a combination of scaffold, Embryonic Stem Cell (ESC)-derived meniscal progenitors and growth factor embedded in the scaffold. This would be a tissue engineering alternative to an allograft (meniscus from a donor) or a cell-free artificial scaffold. • If successful, the approach would result in a clear candidate for clinical development and for the treatment of an unmet need. • Exciting candidate.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• Stem cell therapies for orthopaedic clinical targets have relied on the use of mesenchymal stem cells (MSC) from bone marrow or adipose as these are relatively easy to isolate, do not form teratomas, and even in an allogenic setting are unlikely to be immune-rejected due to their immunoregulatory properties. • However the applicants have avoided MSC for their meniscal repair approach because of the inherent risk of becoming hypertrophic and because of the challenges in ensuring consistency between batches. • The applicants have opted therefore to use ESC as a means of generating MSC because they are less likely to undergo hypertrophy and they have a consistently good potential to generate meniscal fibrocartilage. iPSC were considered to be too variable in an autologous setting. • Many of the short-comings of the original proposal have been fully addressed in this resubmission. There remains some doubt about the potential for immune rejection of ESC-derived MSC, however the applicants have gone some way to addressing these concerns and mitigating the risk through design of the in vivo work. • The preliminary data in the revised application is clarified in some cases. Immune rejection may still be an issue as the implanted cells are likely to be quite different than fresh or frozen allografts This should be tested in the animal models.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**

Yes: 12	• Overall, the project is well designed and can deliver results.
	  ◦ Milestone 1 is proof of concept, including expansion fo the cell line, optimization of tissue engineering in vitro and of ex vivo meniscal regeneration. The meniscal regeneration will be analysed by immunohistochemistry (for quality of the repair tissue) and mechanically (for stability of the new tissue).
	  ◦ Milestone 2 is in vivo proof of concept in a small atopic animal model and a small animal meniscal injury model. The atopic model will assess tissue formation (histologically) and safety (inflammation). This model will involve xenogeneic implantation of the human ESC in small animals.

	● A final aim will be to scale-up implant size in readiness for implantation in large animal meniscal tears at the translational stage. ● The project is well designed to take the product to the next step. However, if growth factor delivery is needed to make the product work, it will create many additional elements to test (e.g. type and dosing). ● The applicant still seems not to have consulted a statistician. They continue to use the Bonferroni correction, which is not appropriate. Nevertheless, perhaps this proof-of-concept study doesn't need rigorous statistics. ● The authors have addressed many of the concerns raised in the first review. ● A small risk of teratoma formation also exists. This should be tested.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 12	● A few pitfalls are suggested with some proposals to work them out. Most of the work appears to have been previously done, so the applicant is unlikely to encounter major issues. ● The proposed milestones are reasonable and likely to be achieved. Previous CIRM-funded work was completed on time. The team is already in place. ● It is not clear if the meniscal injury model has been established in this lab. There is a short time window if this model needs some development. ● The meniscal injury model seems not to be established - this should be addressed. ● The project is challenging in terms of in vivo studies but feasible.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 12	● The writing in the proposal is attentive to serving the needs and underserved communities. ● The product is derived from only one cell line; if successful, this would not limit its use in any population. ● Mensical tear affects all communities.
No: 0	*none*

Application #	DISC2-13072
Title (as written by the applicant)	Providing a cure for sphingosine phosphate lyase insufficiency syndrome (SPLIS) through adeno-associated viral (AAV) mediated Sphingosine-1-Phosphate Lyase 1 (SGPL1) gene therapy
Research Objective (as written by the applicant)	AAV-SPL 2.0 is a gene therapy cure for SPLIS, a lethal childhood disorder of metabolism that causes kidney failure. Our gene therapy may also work in more common fibrotic (scarring) kidney diseases.
Impact (as written by the applicant)	Our treatment may cure a rare but often fatal genetic disease (SPLIS) for which no specific treatment is available. It may additionally cure other forms of kidney disease caused by kidney scarring.
Major Proposed Activities (as written by the applicant)	• Test the ability of our gene therapy to prolong survival in a newborn small animal model of SPLIS. • Test the ability of our gene therapy to protect the kidney from damage in an adult small animal model of SPLIS. • Test the ability of our gene therapy to protect the kidney from damage in small animal models of more common forms of kidney fibrosis. • Use small animal models to demonstrate where in the body our gene therapy can reach and restore the activity of the enzyme encoded by the gene. • Test the ability of the gene therapy to restore sphingolipid metabolism in small animal models of SPLIS.
Statement of Benefit to California (as written by the applicant)	AAV-SPL 2.0 gene therapy may cure children with SPL insufficiency syndrome (SPLIS) and individuals with kidney disease arising from many common conditions and that can lead to chronic kidney disease and kidney failure. Patients with SPLIS have been diagnosed in California. Chronic kidney disease affects 3% of Californians, with higher rates in areas of agricultural work. It is more common in adults aged 65 and older and more common in Black and Hispanic adults compared with white and Asian adults.
Funds Requested	$1,463,400
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All Grants Working Group (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	4
Highest	93
Lowest	80
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	11
(1-84): Not recommended for funding	4

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 proposal have the necessary significance and potential for impact?
Yes: 15	• Sphingosine phosphate lyase insufficiency syndrome (SPLIS) is a rare inborn error of metabolism caused by recessive mutations in sphingosine phosphate lyase 1 (SGPL1). This is a devastating disease with no treatment. • The proposal seeks to optimize an adeno-associated viral therapuetic for SPLIS. Currently there is no specific treatment for this condition. There are published data (JCI Insight) by these investigators to support a level of efficacy in the first-generation therapeutic. Thus this project is likely to result in a candidate which could be quite impactful for these patients. More broadly, we need proof of concept for gene therapies for the field. • This will impact a small group of potential patients, but it's a game changer. • Yes. Gene therapy for SPLIS is the only option for patients with SPL deficiency.
No: 0	*none*
GWG Votes	**Is the rationale sound?**

Yes: 14	• The rationale is sound, as the only way to treat diseases like this is to cause cells to express increased levels of the missing enzyme.
	  ◦ The applicant's viral construct promotes SPL expression and activity and lowers plasma and tissue sphingolipids.
	  ◦ They have an appropriate small animal model for studying the effects of SPLIS in the brain.
	  ◦ They were able to achieve a striking increase in survival in their small animal model, as well as improved neurodevelopment and reduced inflammation in these animals.
	  ◦ There are also beneficial effects of the treatment on SPLIS nephrosis.
	• The project is based on reasonable rationale and is supported by the recent publication(s). One strong general rationale is the lack of an existing therapy. As this is an inherited disorder, gene therapy is a sensible approach. However, the rationale for looking at other diseases (fibrosis, CKD) is weak.
	• The preliminary data are supportive but further development work is needed to understand the range in which this therapeutic approach might be efficacious.
	• I have no concerns. The proposal includes a great amount of preliminary data.
	• Good preliminary data.

No: 1	*none*
GWG Votes	**Is the proposal well planned and designed?**

Yes: 12	• It is appropriately planned overall, particularly the parts focused on SPLIS.
	  ◦ The biggest concern is that delivery to the kidney may not work. Plans for this pitfall are not adequate.
	  ◦ A deeper dive into the AAV-SPLIS approach would be valuable. The applicant should explore where it is expressed exactly (using clear surrogates) and for how long, differential tropism of serotypes, safety issues at higher doses, and the potential value of gene editing versus the traditional AAV approach the applicant proposes.
	• The project appears to be well designed to achieve a candidate suitable for translational studies.
	• The project is very thoughtfully constructed and the data are well chosen.
	• The project plan is commensurate with the mission of CIRM

	• Well thought out. • The timeline is reasonable and laid out in detail. The milestones, however, include too many disease models without strong justification. This could bog down the project.
No: 3	• The models of kidney fibrosis outside of SPLIS are a distraction and need not be part of this proposal. • More experimental focus on the therapeutic candidate is needed. • AAV delivery into the kidney is not trivial.
GWG Votes	**Is the proposal feasible?**
Yes: 14	• One aspect that was not sufficiently addressed was whether/how exactly the therapeutic can get into the kidneys (and a plan to troubleshoot if it cannot). Tropism of different AAV may need to be tested using a surrogate to complement immunofluorescence analysis of the target. The aims to look at multiple mouse models of kidney disease seem premature and can be scrapped - better to get one drug through than ten in development. • The applicant pays careful attention to various problems in SPLIS, and provides an analysis of a sufficient number of outcomes to give confidence moving forward. Attention is also paid to potential other uses of the viral construct. • The proposed milestones and outcomes are likely to be achieved. • Yes, the team is very well qualified for this project. Many years of experience studying the lyase. The one weak point is that there is does not seem to be substantial previous expertise in AAV drug development. • The team is extremely well-qualified to carry out this work. • The applicant is the leader in SPL biology, from identifying the gene encoding sphingosine phosphate lyase (SPL) to describing the clinical syndrome. All the expertise required to complete the proposed studies is in place. • I have no concerns; the preliminary data are strong. • All the necessary resources are available. • The applicant has already developed several of the models and reagents. • The budget is more than sufficient for this type of work. The research team is a bit large relative to the scale of the work (which is in mouse). Some of the assays do require specialists and the AAV are expensive. The budget is detailed. • The budget is appropriate.
No: 1	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	• Potentially yes, as the disease does not discriminate. Thought has been given to sequencing diverse populations. It is worth thinking about whether California or the federal government will subsidize an expensive gene therapy based on socioeconomic considerations. • SPLIS has been identified in patients of the world of both genders. • No concerns.
No: 1	• Not clear; just a small number of patients is described.

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Application #	DISC2-13205
Title (as written by the applicant)	iPSC-derived smooth muscle cell progenitor conditioned medium for treatment of pelvic organ prolapse
Research Objective (as written by the applicant)	Conditioned media from human iPSC-derived smooth muscle cell progenitors. This media exerts a paracrine effect to restore damaged vaginal wall in patients with pelvic organ prolapse.
Impact (as written by the applicant)	Pelvic organ prolapse (POP) is characterized by the downward movement of the vagina and/or uterus through the vaginal opening. It is treated with surgery. The candidate is a non-surgical treatment.
Major Proposed Activities (as written by the applicant)	• Production and banking of conditioned media from human pluripotent stem cell-derived smooth muscle cell progenitors • Develop measures of identity and activity. • Demonstrate reproducible disease/injury modifying activity in three human iPSC lines and two human embryonic lines. • Perform initial studies to assess mechanism of action and early safety.
Statement of Benefit to California (as written by the applicant)	Pelvic organ prolapse affects adult women. Northern Californian studies show that Latinx and white women have a 4-5 times higher risk of symptomatic pelvic organ prolapse compared to African American women. The candidate addresses the unmet medical needs of CA women. It can be produced in quantities sufficient for multiple use and stored. It is easily injected into the vagina by the gynecologist in the office. This decreases overall cost and morbidity compared to current surgeries.
Funds Requested	$1,420,200
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 proposal have the necessary significance and potential for impact?
Yes: 13	• Pelvic organ prolapse (POP) is a serious condition with few therapeutic options and concerns over safety of some longer-standing approaches to treatment. The proposed therapeutic would offer an alternative approach. • The candidate is conditioned medium from autologous iPSC-derived SMC progenitors which it is proposed will treat pelvic organ prolapse. Current treatments are sub-optimal and there are no preventive treatments so the candidate would address an unmet medical need. • Conditioned medium from human iPSC-derived smooth muscle cell progenitors containing bioactive factors secreted by the cells may exert a paracrine effect restoring function in women suffering from pelvic organ prolapse. This is an important unmet need as current treatments are not always effective. • The proposal is to generate conditioned medium from autologous iPSCs for injection into the vaginal wall once weekly for three weeks. • The product would be easy to apply and likely cost-effective compared to surgery. The product could be easily and likely quickly translated to clinical trials. • Important application with high clinical relevance • The proposal has potential to be of significant impact but the rationale for using autologous iPSCs rather than donor iPSCs is not clear. • The reason for using autologous patient-derived iPSCs to generate the product is not clear. Why not use donor cell lines?
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• The premise of the study is based on the sound scientific rationale that current treatment for POP is sub-optimal and the preliminary data that the product is beneficial in both in vitro and in vivo models of urethral and vaginal injury. • The rationale is logical and based on a body of literature as well as preliminary data for urinary incontinence. The overarching hypothesis is that secretomes in the conditioned media (CM) from pluripotent stem cell-derived smooth muscle cell progenitors will restore the damaged vaginal wall. • Preliminary data shows a hint of efficacy. • Data are provided demonstrating effective differentiation of iPSCs or ESCs to smooth muscle cells (SMCs). • Supporting preliminary data is provided demonstrating that the investigators have the model systems and that the product is beneficial in both in vitro studies and a rat model of urethral and vaginal injury. • In a rat model of urethral/vaginal injury, injection of the product improved leak point pressure compared with sham-treats animals. The improvement though was modest and only significant for two out of three of the preparations tested. • The improvements observed in the rat model were accompanied by an increase in the density of smooth muscle cells observed histologically. • Secretome analysis from iPSC derived smooth muscle cells revealed some common factors expressed at high level. These proteins could be used as identity/potency markers. • The idea is sound, but not convinced re-programming cells from a person with POP will solve the problem. I think an off-the-shelf product will be better. • Tissue sampling is not clear. • No preliminary data are presented for vaginal prolapse repair.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**

Yes: 13	• This is a resubmission. The investigators have addressed the majority of the previous comments and the overall design and aims are greatly improved. • Previous critiques were adequately addressed. • The project is logically planned and the proposed aims should achieve a candidate to advance to translation. • The investigators have the expertise and models to complete the proposed aims and to confirm the therapeutic potential of the candidate. • The in vivo outcomes are the strength of the study. • The project will depend on directed differentiation of iPSCs or ESCs to SMCs in order to generate secretome from the derived muscle cells. Further analysis of highly expressed proteins will be undertaken for the identified candidate markers. • Use a defined medium (rather than FBS) might yield more consistent data. • The use of animal products (e.g. FBS) is a concern when a more defined medium would be more appropriate and meet GMP. • Use of young rats may cause two issues. Young rats heal quickly and so the separation between treatments may be small and the treatment may not be effective in older rats. I would include a group of older rats with the candidate. • Age of rats needs to be adapted to recapitulate the target population. • Dose response testing is required, e.g. testing different concentrations of CM is missing. • The high variability between the different cell lines is a concern, and there maybe synergy between low/moderately expressed bioactive proteins and this is not addressed. • Pitfalls are addressed but alternatives if no common high expression bioactive proteins in conditioned media from different cell lines are observed or immunodeficiency effects outcomes in the rat model are not considered. • Safety will be assessed in a tumorgenesis study in severely immunocompromised animals. • Durability studies will be important. • Care should be taken when selecting tissue for Milestone 4. Sampling of tissue both near and away from injury sites will be important. Tissue selection should also include sites near injections and remote from injections.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 13	• The milestones and expected outcomes can be successfully achieved within the proposed timeline. • Highly productive physician scientists with the necessary expertise to complete the project. The PI is an expert in molecular pathophysiology of urinary incontinence and the co-investigator will bring expertise in muscle contraction measurements. • Strong team. • The animal model is new and will present some difficulties in achieving a consistent model, but because they will start this early in the timeline this shouldn't slow the project down. • The project is feasible. The previous study of urinary incontinence gives some evidence for efficacy, although the effect was modest and no data are yet available for vaginal injury. • Pitfalls not well discussed.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	• Applicant describes the likely benefit to underserved communities. • The project adequately addresses race and ethnicity and the candidate will help women who have pelvic organ prolapse including those in the underserved communities. • The project would be beneficial to underserved communities as the treatment would be easy to implement. • Institutional commitment to DEI is well described.

	• Prevalence is higher in white and Latina women and this will be reflected in the choice of cell lines. • They will be testing stem cells from 2 different ethnic groups. I think this is a good start, however, if there are some economies of scale, adding an additional line or two should be considered. • Work is with female animals due to the target indication.
No: 0	*none*

Application #	DISC2-13102
Title (as written by the applicant)	RNA-directed therapy for Huntington's disease
Research Objective (as written by the applicant)	We develop a novel adeno-associated viral (AAV) vector-delivered RNA-targeting therapeutic for elimination of toxic RNA causative of Huntington's disease.
Impact (as written by the applicant)	There are no disease-modifying therapies for Huntington's disease. Our therapeutic, if successful, will be a first-in-class treatment for this invariably fatal neurodegenerative disorder.
Major Proposed Activities (as written by the applicant)	• In vitro studies of the RNA-targeting system in human Huntington's disease patient stem cell derived striatal organoids to assess the ability to eliminate toxic RNA foci • AAV vector packaging of the CAG-targeting RNA-targeting system to obtain high-titer viral preparations, and in vivo (small animal model) safety studies to assess immunogenicity, cytotoxicity and off-target effects • In vivo efficacy studies of the RNA-targeting system in a mouse model of Huntington's disease to assess effects on disease-relevant molecular, cellular, behavioral and motor function deficits
Statement of Benefit to California (as written by the applicant)	Currently, there is no cure for Huntington's disease, which currently affects thousands of Californians. The California population will equitably benefit from the development of a therapeutic for Huntington's disease, which affects the state's residents roughly equally across gender, race, ethnicity and socioeconomic status. Our therapeutic strategy is readily transferrable to a large set of other devastating diseases, multiplying the benefits of development of this new therapeutic modality.
Funds Requested	$1,408,923
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All Grants Working Group (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	1
Highest	87
Lowest	83
Count	12
(85-100): Exceptional merit and warrants funding, if funds are available	11
(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 proposal have the necessary significance and potential for impact?
Yes: 11	• Huntington's Disease (HD) is incurable and represents a high need. Antisense oligonucleotides (ASO; a DNA-based therapy) have failed to show efficacy in clinical trials for Huntington's disease. Increasing efficacy using ASO is problematic as ASO cannot cross the blood-brain barrier, have a short half-life and thus must be administered monthly through a highly invasive procedure. • The Principal Investigator (PI) is co-founder and scientific advisor to a biotechnology company with an exclusive license for this technology. The company has raised over $150 million from venture financing to bring therapeutics to the clinic. • There is currently no efficient or disease-modifying treatment for HD and the proposed therapy would impact an unmet medical need. • This proposal is within CIRM's stem cell scope as it uses striatal brain organoids for screening the candidate in one of the early milestones. • Yes. Recent oligonucleotide trials for HD have failed, so a new approach is needed. • Why would this approach have benefit when ASO have failed? • The proposal describes a great alternative strategy to ASO.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 11	• The idea is to target toxic huntingtin repeat expansion transcripts for degradation using an RNA-directed nuclease. • The investigator proposes an alternative strategy to CRISPR-based gene editing to avoid potential detrimental responses of the innate immune system to a bacterial-derived CRISPR system protein. Instead, they developed an antisense RNA system entirely derived from human proteins. The PUF protein supports elimination of repeat expansions when fused to an RNA endonuclease. • The investigator developed a novel AAV serotype - AAV-PHP.eB20 - in order to provide broad expression of the PUF-PIN system throughout the brain via intravenous injection. This viral vector has been shown to efficiently transduce the cortex and striatum, two brain regions with HD pathology. • While the applicant does not provide data that show successful targeting in vivo, recent reports indicate that this viral serotype can be used to efficiently express a transgene in the central nervous system (CNS) via intravenous injection in both small and large animal models. • In their description of the AAV-PHP.eB virus, the applicants state that this virus results in improved cortical and striatal transduction, however, they do not discuss which other regions may be affected. Huntingtin is expressed throughout the body and there may be value to decreasing levels in multiple regions but the possibility of peripheral toxicity or reduction in huntingtin should be addressed in the safety experiments, especially given that potential for severe liver disease. • The choice to target CAG repeats is likely to result in significant off-target affects of the complex given that wild type huntingtin and several other normal proteins contain CAG repeat expansions larger than eight. • While the applicants acknowledge recent failures of antisense-oligonucleotide trials in HD, they claim that the lack of success is due to failed target engagement and major side-effects provoked by the intrathecal route of delivery. However, one very important observation from this trial is that CSF huntingtin levels were lowered by 60%, without any indication of clinical benefit in patients. Given that the applicant's approach has a similar

	mechanism of action, they should address the possibility that the reduction of huntingtin may not be sufficient to generate improvements. • The rational is sound. However, it is not clear that targeting of neurons is sufficient for disease-modifying efficacy, Reduction of huntingtin protein levels in cerebrospinal fluid (CSF) by as much as 40% was not effective using ASO - is it known how CSF levels relate to brain levels of huntingtin? There seems to be an unproven hypothesis that ASO did not sufficiently alter brain levels of huntingtin - are their alternative explanations for the failure of ASO that should be considered? • The authors have also developed a protocol for striatal organoid differentiation which has been successfully completed using (induced Pluripotent Stem Cells) iPSC from control and HD patients. The striatal identity of the cells is supported by immunofluorescence data which shows that DARPP32+ cells are present. • One major issue with this grant is that the applicants do not seem to have a good grasp of HD disease or pathology. This is exemplified, in part, by their choice of animal model and their description of this animal model. For example, the timeline of disease progression in the R2 small animal mouse is much more rapid than the timeline of experiments proposed by the applicant (up to a year, when the animals typically die at three months of age). In the HD field, it is now mandatory to conduct in vivo work in at least two, if not three, distinct genetic models of the disease if meaningful data is to be expected and translated to the clinical setting. Milestone 3 of the grant is therefore built on shaky grounds. A collaboration with an established HD group would be recommended.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**

Yes:
10
	• Overall, yes. My specific comments are
	  • Preliminary data show that the team possesses the necessary skills to produce organoids that express markers of striatal identity using control and HD iPSC cells. HD striatal organoids reproduce increased extracellular glutamate concentration. However, gene expression of other markers is not consistent (e.g. BDNF, TFAM, PGC1a) between HD53 and HD109 and it is unclear how this will affect disease modeling using these organoids (Figure 4).
	  • In Figure 6, the applicants show medium spiny neurons labeled with a AAV9-DLX-eGFP but an immunofluorescence analysis using markers specific for this cell population would help confirm the proper identification of the neuronal subtype.
	  • The team has already produced an HD-PUF-PIN that reduces Exon1 HTT CAG repeat RNA in HEK293T cells (Figure 5). However, this test was performed in an overexpression system and only exon1 HTT was evaluated. This is an early proof-of-concept experiment and therefore remote from the clinical situation.
	• The preliminary data cover multiple aspects of the project including development of a construct to reduce HTT levels, organoids from HD patient iPSC, as well as their characterization. While data are included, important details are lacking.
	• To measure the change in cognition in the animal proof of concept studies, the applicant's plan is to use the Montreal Cognitive Assessment (MoCA). But the MoCA not very sensitive. Please compare and contrast this choice with other possible outcome measures.
	• Should Milestone 3 be completed before Milestone 2? The rules for stopping seem to depend on endpoints from Milestone 3, and not on the safety data from Milestone 2.
	• The proposal's focus on one suboptimal small animal model is a weakness.
	• Discuss the pros and cons of the choice of mouse model.

No: 1	• The proposal should include proof of concept and safety testing in more than one small animal model. Consultation with an HD expert would be helpful.
GWG Votes	**Is the proposal feasible?**
Yes: 11	• The project is well planned, with a logical succession of steps from in vitro to in vivo validation. By the end of this grant, the applicant anticipates to identify a safe and effective gene therapy approach that improves on current technologies by using a human-based system instead of a bacterial CRISPR platform. However, the proposed small animal model testing does not meet the recommendations within the field for translation to

	clinical trials. Furthermore, the small animal model selected overexpresses an exon1 transgene making it very distinct from the expression pattern in patients. Demonstration of low toxicity or high efficacy in this model is unlikely to generate data that will be clinically meaningful.
	● This is a well constructed project that proposes a clear roadmap to develop a novel therapeutic for HD. However, a few key details are missing:
	  ● The proposed viral vector will specifically target the CNS, but huntingtin is ubiquitously expressed in both the brain and periphery. It is unclear that CNS reduction of huntingtin levels will be enough to prevent or treat HD.
	  ● The applicants use iPSC with a wide range of CAG repeats; however the lowest repeat number (53) is still above average for the clinical population. If the tested vector preferentially targets expanded repeats, this could be problematic given that the small animal model also has highly expanded repeats. It would be useful to include a lower expansion iPSC line to confirm that a reduction in huntingtin levels is still possible when the repeat length is shorter.
	  ● In the in vivo safety studies, the applicants state they will look for a balance between on-target and off target affects. The section seems to imply that they intend to target all proteins with a CAG repeat locus. Such a broad approach raises concerns about unintended effects.
	  ● The selection of the small animal model of HD is problematic and the study design indicates a lack of familiarity with this system. The applicants intend to follow the mice for 12 months, despite the fact that the mice generally do not survive beyond 16 weeks.
	● In vitro organoid experiments are planned over a period of just six months. However, preliminary data uses organoids that require three months to prepare. It seems overly ambitious the team will be able to collect all necessary data across six HD patient lines in six months.
	● The principal investigator is a leader in the use of CRISPR technologies to perform gene correction in disease models.
	● Endpoints of the experiments are well defined.
	● Potential liver toxicity should have been discussed
	● The applicant team includes experts in the field.

No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 11	● A cohort study found a significant association of Huntington's disease diagnosis frequency with socioeconomic status, with higher rates of diagnosis in persons with lower annual household income. Therefore this therapy would serve a need of this underserved community. ● The proposed therapy would serve all patients regardless of ethnicity but the cost may be a barrier to broad access. ● Huntington's disease affects a broad array of individuals, and this project would serve them all.
No: 0	*none*

Application #	DISC2-13131
Title (as written by the applicant)	A Novel Therapy for Articular Cartilage Autologous Cellular Repair by Paste Grafting
Research Objective (as written by the applicant)	Articular paste graft containing Mesenchymal Stem Cells (MSC) and an adhesive hydrogel that support cartilage growth will be combined for an effective and functional stem cell based cartilage repair procedure.
Impact (as written by the applicant)	The proposed biologic cartilage repair therapy results in accessibility of an effective, low cost, one-step and functional biologic solution to those with cartilage injuries and arthritis.
Major Proposed Activities (as written by the applicant)	• Optimize preparation of articular tissue-derived paste graft containing autologous MSC / stromal cells. The addition of allogeneic MSC will be assessed in optimized formation of cartilage constructs. • Optimize mechanical and cell-viability properties of hydrogel adhesion and fixation of the paste graft within articular defects. • Determine preliminary safety and effectiveness data of the method in a rabbit model of cartilage repair and assess feasibility in a goat model of cartilage repair.
Statement of Benefit to California (as written by the applicant)	The successful outcome of this project will be to: 1. Provide an effective surgical solution to osteoarthritis and traumatic cartilage injury to the broad spectrum of the California patient population. 2. Develop a surgical kit used in the surgery that can be distributed and sold nationally and internationally, bringing revenue and jobs to California. 3. Reduce overall healthcare costs due to a simple, single-step surgical technique that provides long term reduction in pain and increased function.
Funds Requested	$1,316,215
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All Grants Working Group (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	84
Median	85
Standard Deviation	5
Highest	88
Lowest	65
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	14
(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 proposal have the necessary significance and potential for impact?
Yes: 13	• Current therapies for cartilage defects are expensive and limited to small sized lesions. There is a clear need for lower-cost therapies and for therapies for large articular lesions. The proposal builds on an optimized and established technique that utilizes endogenous bone marrow MSC as part of an autologous paste graft. Addition of allogeneic MSC to enhance the product will also be explored. The project is logically designed and will progress to translation in clear steps. • Cartilage is the connective tissue that covers our mobile joints (e.g., knee, hip, shoulder). Since it is avascular, it has a poor intrinsic healing capacity. Untreated lesions of the cartilage surface can lead to osteoarthritis that afflicts 70% of the population over the age of 65. A methodology to successfully delay the use of joint prosthesis (i.e., implant), with a lifespan of 10-20 years, would be clinically important for younger patients who have significant cartilage damage from trauma or with arthritis. • The candidate graft paste-hydrogel-MSC combination is a minimally invasive, in situ polymerizable graft to fill and fix some types of cartilage defects. The approach is intended to augment the microfracture cartilage repair technique that is currently indicated for small defects, and thus expand its utility to larger defects. Hopefully this will lead to better long-term outcomes. • The candidate is an autologous graft that provides chondrocytes as well as MSC from osteochondral grafts that are morselized into a graft paste, augmented with additional MSC, and applied to the defect to augment microfracture repair of the lesion. 'Microfracture' is micro-drilling of the bone plate underlying the articular cartilage layer, which permits bone marrow (with MSC and blood) to ooze up repair cartilaginous tissues. The candidate graft paste includes a biocompatible hydrogel containing cartilage extracellular matrix (ECM) and chondrocytes. This hydrogel may promote a chondrogenic phenotype among the MSC within the paste and the MSC introduced from bone marrow. The strategy may result in the formation of hyaline cartilage tissue, which is superior to the fibrocartilage tissue that is typically formed with the microfracture approach alone. • If successful, this therapy would be impactful, improve quality of life, and likely reduce lifetime costs. The approach could be used to treat larger lesions. • The translation phase will be supported by collaborations that the applicant has in place. • The hydrogel components used in this approach are currently FDA licensed and used in several tissue engineering applications. • No concerns.
No: 1	• The proposed procedure may exploit the regenerative potential of cartilage and bone-derived MSCs for cartilage repair. • It is not clear whether the efficacy of the proposed candidate for cartilage repair is comparable or superior to other current strategies. • The idea behind this proposal is to simplify the surgical procedure but the over ambitiousness and the lack of details of the proposed work will unlikely simplify the current procedure which according to the applicants is already successful. • The proposal does not include discussion of future steps for translation.
GWG Votes	**Is the rationale sound?**
Yes: 13	• The approach is supported by literature findings, publications from the team, and preliminary data. • The project seeks to address the limitations of the applicant's existing osteochondral graft paste. Follow-up studies of hundreds of patients have shown that the surgical procedure using the current graft paste is difficult, and that the

	procedure has a one-in-three success rate. Therefore the existing graft paste is not suitable for widespread adoption. • The new approach is bolstered by scientific literature providing sound rationale to introduce MSC (Bian, Tissue Eng A, 2011) and the specific hydrogel carrier (Sharma, Sci Translational Med, 2013). • Preliminary data support the critical aspects of the proposal. • Clinical studies of the applicant's existing autologous graft paste procedure (with 10 to 23 years of follow up) show that the therapy is associated with improvements in patients' pain and function scores, and with enhanced chondrocyte mobility, proliferation and gene expression indicative of cartilage regenerative capacity. • The rationales for (1) using a bondable hydrogel to stabilize the repair at the site of the microfracture, and (2) including cellular sources of cues to promote appropriate MSC differentiation, are both reasonable. • Yes. The project builds on an existing approach involving MSC naturally occurring in paste graft, here potentially enhanced using allogeneic MSC. • The applicant has over two decades of experience using a paste graft approach. • Previous clinical outcome data show graft survival and benefit for an average of 16 years, and a delay in time to arthroplasty until an average age of 60 years. • Evidence is provided that the new paste graft contains MSC in the cartilage and bone marrow component. • Evidence is also cited to show that paste graft cells can generate cartilage when seeded onto scaffolds and cultured in vitro and that the crushing of grafts activates chondrocyte formation and proliferation. • The applicant has developed a fiber-reinforced hydrogel with compressive, tensile and permeability properties that resemble native cartilage. Importantly, the hydrogel does form when in contact with the lesion, and UV light activates covalent linkage of the hydrogel to surrounding cartilage and bone with appropriate tensile strength. • There is some in vivo evidence for successful repair using the current graft paste in a large animal model with 4 months of follow-up. Seeding of the paste hydrogel with chondrocytes supported cell growth and cartilage formation. • Yes. However it is not clear that this proposal has a high degree of focus on stem cells. • There is a strong clinical team with high translational potential. • Clinical data are supportive.
No: 1	• Neither the proposal nor the applicant's published studies directly address how efficacy or cost of the current approach will compare with existing procedures. • In existing autologous paste graft procedures, the repair tissue is frequently composed at least in part of fibrocartilage rather than the hyaline cartilage found in normal joints; it is not clear how the proposed approach will address this limitation. • The proposal aims at facilitating surgical repair of damaged cartilage using autologous tissue that contains a small percentage of MSC.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 12	• The project plan is logical and milestone outcomes for the in vitro and in vivo aims appropriate. The proposal takes care in motivating and spelling out the experimental design - groups, conditions, variables to be manipulated. Outcomes and methods are listed with reliance on description through team publications, expertise via biosketches, and preliminary data. • As presented, the proposed research is achievable with relatively low risk and offers a great opportunity to get meaningful and important data. Accordingly, there are no real pitfalls identified and the experimental design is comprehensive in terms of the parameters studied. • The current graft paste (i.e., without hydrogel) works about one third of the time (according to the applicant). With a more consistent formulation, introduction of MSC, and hydrogel to provide ease of handling and help stabilize the repair, outcomes would be expected to improve.

	• Yes. By the end of the proposed milestones, the applicant should have small animal model data on safety and efficacy and large animal model data on feasibility. If supportive, these data will enable translation of the approach to a preclinical large animal study of cartilage repair suitable for regulatory evaluation. The team has the clinical and regulatory experience to translate the technology to patients. • The project is well designed: In vitro development; followed by testing in a small animal model at 4 months (previously shown to be predictive of 12 month outcome in this model); followed by preliminary trials in a large animal model with 1 month follow-up in preparation for the translational phase. • Depending on the Food and Drug Administration (FDA) designation of the graft paste-hydrogel-MSC product, it seems that the product could be designed using autologous or allogenic tissues or cells. It is not clear what the plan is clinically in terms of getting MSC to augment the paste. In this proposal, human cells derived from bone marrow are purchased from a vendor for in vitro experiments. Moreover, the MSC populations could be derived from fat or synovium. Additional MSC may not be needed and will increase cost. • The project is very well designed and likely to deliver results. • The timeline is appropriate; the appropriate urgency is built in; and there is a clear route to translation. • Pitfalls have been considered and decision points built in.
No: 2	• The preliminary data are not detailed and are mostly qualitative, consisting mostly of single surgical and technical pictures. There are few quantitative data. • The proposal includes largely qualitatively data, lacks experimental details, and lacks measured outcomes. • This is very ambitious plan with an aggressive timeline. • Potential pitfalls and alternative approaches are not discussed. • Milestone 1, task 1: Multiple methods are proposed with few details. • Milestone 1, task 2: Details are missing on how the paste will be used for tissue engineering in vitro. • In Milestone 2, multiple conditions will be tested in parallel without preliminary data for the feasibility of such an ambitious approach. • The Proposal has multiple figures with same label (two Figures 3, two Figures 4).
GWG Votes	**Is the proposal feasible?**
Yes: 12	• Expertise in orthopedic surgery, cartilage tissue engineering, regulatory affairs in biotechnology, and cartilage biomechanics are appropriately represented. The technical staff are well-qualified and experienced with cartilage analyses. • The budget is appropriate. The key personnel are qualified and have committed adequate percent effort to the project. • The team has a track record of generating the components necessary for the proposed project. • The expertise and physical resources are available to complete the proposed studies. • The project is feasible and has a reasonable chance of success.
No: 2	• The milestones are overly ambitious and some studies lack quantitative outcomes. • Who will perform the proposed experimental research?
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 14	• At present, stem cell based procedures cater to a limited section of the population with access to expensive procedures and long periods of leave from work. The proposed procedure has the potential to provide relatively inexpensive stem cell based articular cartilage repair and enhance orthopedic health equity among patients in California and the United States. • The proposal articulates how osteoarthritis incidence is higher in women and in African Americans, and people in occupations involving manual labor. The small animal model studies will focus on female rabbits for this reason. • Osteoarthritis is unduly prevalent amongst under-served communities.
No: 0	*none*

Application #	DISC2-13013
Title (as written by the applicant)	Optimization of a gene therapy for inherited erythromelalgia in iPSC-derived neurons
Research Objective (as written by the applicant)	The goal of this grant is to develop a gene therapy for a rare painful disorder, Inherited Erythromelalgia (IEM).
Impact (as written by the applicant)	There are currently no Food and Drug Administration (FDA)-approved drugs for IEM, which is caused by a gain-of-function mutation in a sodium channel, Nav1.7. We propose epigenetic repression of Nav1.7 to provide a cure for IEM.
Major Proposed Activities (as written by the applicant)	• We will characterize the lead gene therapy candidate that will move into IND-enabling studies. • We will determine the efficacy of this lead candidate in a clinically relevant human cell population (from patients with Inherited Erythromelalgia). • We will perform dose range studies to provide preliminary identification of the target organs of toxicity as well as to select doses for future definitive toxicology studies in non-human primates. • We will request an FDA meeting.
Statement of Benefit to California (as written by the applicant)	It is estimated that 50 million Americans suffer from chronic pain, with patients relying mostly on opioids. In California, an estimated 45% of drug overdose deaths involved opioids in 2018. We are in dire need of new treatments for chronic pain. Although our first indication will be a rare painful condition, our gene therapy could potentially benefit other individuals with intractable painful conditions, as the gene we are targeting is involved in pain transmission and in many pain conditions.
Funds Requested	$1,157,313
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All Grants Working Group (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	84
Median	85
Standard Deviation	4
Highest	95
Lowest	78
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	7
(1-84): Not recommended for funding	6

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 proposal have the necessary significance and potential for impact?
Yes: 13	• Strengths: (1) if successful, this project may lead to the development of a treatment for Inherited Erythromelalgia (IE); (2) encouraging preliminary results; and (3) nice progression of Milestones. • Concerns: (1) inadequate description of what patient-specific induced Pluripotent Stem Cell (iPSC) lines will be used in Milestone 2; and (2) no apparent expertise in the derivation of neurons from iPSC. • The candidate is an AAV gene therapy for epigenetic repression of Nav1.7 that will reduce chronic pain in IE patients, for whom treatment is currently very limited. • Impact on pain management has enormous implications, chronic pain is a large unmet need - the proposal has the potential to limit or eliminate demand for opiates. • This is a risky but potentially transformative approach to pain. • The candidate shows strong promise for a new type of therapeutic. • Chronic pain is a large problem. • This would be a major advance.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• The rationale that Nav1.7 repression can reduce chronic pain is sound based on the strong preliminary data presented and published data. • Preliminary data are compelling. • Strong preliminary data. • The rationale is solid.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 10	• The project fits with the expected outcomes of the program announcement and is appropriately designed to develop the candidate and take it to an Investigational New Drug (IND) submission. • Milestone 1 will characterize the different Nav1.7 candidate options for efficacy and specificity using a variety of human cell lines including human Embryonic Stem Cell (hESC)-derived glutaminergic excitatory neurons. Milestone 2 will assess the lead candidates from Milestone 1 in iPSC-derived neurons from IE patients. These are a logical set of aims that should identify the optimal candidate for translation. • Milestone 3 will determine the therapeutic window and Good Laboratory Practice safety in a small animal model of neuropathic pain. While some of these data may be necessary for preparation of the IND, I am concerned that the outcomes may not reflect the clinical scenario in human patients since there is low homology between the mouse and human Nav1 sequence. However, the investigators do comment that they will subsequently progress to non-human primates. • Pitfalls and alternatives are adequately addressed although the limitations of the small animal model in Milestone 3 may be greater than the applicant anticipates. • Patients cell lines are not established and there are no letters of support from collaborators who would provide the patient cells; the source for patient cells is unclear. • Limitations of the small animal model might be more severe than anticipated.
No: 3	*none*

GWG Votes	Is the proposal feasible?
Yes: 11	• This is a highly productive group of investigators with complementary expertise in gene therapy, chronic pain, immunology, genomics, transcriptomics, and stem cell biology. They have a history of successful collaboration • There are no data provided that would indicate that the group can successfully derive iPSC cells from patients. • The milestones, outcomes, and timelines are realistic. • Ambitious proposal, but the progression is reasonable. • Very strong team that is likely to execute the milestones. • One biosketch is missing.
No: 2	• As stated above, I have concern for the feasibility of studies proposed in Milestone 2. As implied in the title of the grant, patient-specific iPSC-derived sensory neurons are an important component of the proposal. The proposal does not indicate that these materials have been identified and secured, and that the team has the expertise to perform studies (no pilot results and no prior experience based on the biosketches). I encourage the applicant to seek a collaborator or consultant and to provide pilot data. • This is a good team, but they don't have the iPSC in hand.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	• The proposal indicates that the applicant will aim to include patients with diverse ethnic backgrounds in the eventual clinical trials. • Sex is addressed but race and ethnicity are not discussed; this is probably due to the rarity of IE in the population overall. • The candidate will benefit the unmet medical needs in all racial/ethnic communities. • The organization embraces Diversity, Equity, and Inclusion (DEI) values.
No: 0	*none*

Application #	DISC2-13221
Title (as written by the applicant)	Development of a novel stem-cell based carrier for intravenous delivery of oncolytic viruses
Research Objective (as written by the applicant)	Develop a stem cell-based platform that safely and efficiently delivers viruses that specifically kill tumor cells and restore immune activity in patients with advanced cancer.
Impact (as written by the applicant)	Overcome the inherent limitations that prevent efficient intravenous delivery of tumor killing viruses to metastatic tumors.
Major Proposed Activities (as written by the applicant)	• Compare the relative efficacy of native or carrier-delivered oncolytic virus to home to, and infect, metastatic breast cancer cells. • Compare the relative efficacy of native or carrier-delivered oncolytic virus to exit tumor blood vessels and escape neutralizing antibodies. • Compare the relative efficacy of native versus carrier-delivered oncolytic virus to specifically infect tumor tissue versus nonmalignant tissue • Compare the relative efficacy of native versus carrier-delivered oncolytic virus to promote objective breast tumor regression and reduce overall metastatic load • Compare the relative efficacy of native versus carrier-delivered oncolytic virus to break cancer-induced immune tolerance
Statement of Benefit to California (as written by the applicant)	If successful, this proposal will provide the necessary data that will enable the design of clinical trials for improved delivery of tumor killing viruses for the treatment of nonresectable, recurrent, or metastatic solid tumors using stem cell-derived biocarriers.
Funds Requested	$899,342
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	83
Median	85
Standard Deviation	4
Highest	85
Lowest	75
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	7
(1-84): Not recommended for funding	7

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 proposal have the necessary significance and potential for impact?
Yes: 11	• Metastatic breast cancer currently has no cure. • The idea is not a cure, but an aid to help reduce metastasis, so maybe not a big hit, but clearly helpful. • Enucleated stem cell-derived carrier cells expressing several markers as a drug delivery system. Carrier cells will deliver oncolytic virus to inflamed sites. • If the carrier cells can both home and protect oncolytic viruses from immune clearance, this could have broad impact as a general approach in oncolytic virus delivery for several cancers. • High probability of success for using carrier cells, but oncolytic viruses would still need to be effective on tumors.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 10	• Carrier cells live for a maximum of 5 days and do not replicate due to enucleation but can traffic to sites of inflammation due to chemokine receptors and adhesion molecules. • Carrier cells can carry oncolytic virus to tumors. In the preliminary data, IV injections and the measurement of localization in lungs (with tumors) after 24 hours is too soon. All cells injected IV will be found in the lungs before trafficking elsewhere. A time course on localization is needed. • There are established methods for quality control of carrier cells. Enucleation is key for safety as demonstrated stable carrier cell generation, and homing to ligands. • Synegic models of breast cancer metastasis represents a good choice for testing homing efficiency and specificity, however, use of in vitro systems for optimization seems unnecessary vs. going directly to in vivo measures. More emphasis on demonstrating normal tissue is not affected, using more in-depth integration eg. size, pathology, and extended periods aside from tumor models (control mice) would improve the proposal and resulting data from a safety context. • Controls missing. Key is the data of rapid accumulation into the lung, but it is unclear if this is unique to engineered cells, and controls should be shown, eg. non-carrier cells, as most cells IV injected go to the lung. • A number of assumptions are not proven or tested.
No: 2	• It is not clear why the cells will not be protected from immune surveillance as they are allogeneic. • The utility of the product is based on the belief that oncolytic viruses will be clinically useful. • So will oncolytic viruses work? Can they really evade the immune system?
GWG Votes	**Is the proposal well planned and designed?**
Yes: 9	• Aim 1 assesses localization of carrier cells and oncolytic virus in tumor cells. • Aim 2 uses a spontaneous metastatic model and will measure anti-tumor activity (primary and metastases) and immune infiltration and immune response. • Experimental plans, including in vivo models, are well-designed and account for level of quantitation using mCherry cells for in vivo imaging. Unclear why in vitro serum experiments for neutralizing antibodies are being tested, vs. direct in vivo studies. • The production and assays, along with data evaluation to create quantitative measured using cellular systems that are complex, is well done. Lots of controls and even double-blind approaches to subjective measures of tumor infiltration measurements. • Not clear if oncolytic virus will kill carrier cells or if carrier cells can respond to apoptosis due to enucleation. • It should produce a product and data to support further development.

	• It is not clear whether the models used are relevant. • It is not clear how the quality of the product will be measured across different production lots. • Given the ease of using carrier cells, if homing does not work, and applicant suggests reengineering the cells and reattempting with new cells. The alternatives for homing are not discussed (how will these be determined?), other than changing number of injected cells. The idea of expressing a marker to block immune attack is thoughtful, and begs why this is not done first.
No: 3	• A suitable control is needed to compare the engineered carrier cells.
GWG Votes	**Is the proposal feasible?**
Yes: 12	• Team of experts are assembled. Clinical oncology expertise for next steps may improve the kinds of data that can be extracted from experimental recipient mice and may improve data sets for patient trials in the future. • Feasibility is provided by accepted paper. • Based on the preliminary data. • Excellent team.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 12	• Applicant "has committed itself to fostering workplace development, diversity, equity and inclusion in research." • Acknowledges diversity but has no specific strategy in the proposal. This project is relevant in many cancers over a widespread ethnic and gender backgrounds. Lots of stats provided, but not much related to this specific proposal.
No: 0	• Needs of underserved communities would not genuinely benefit from this technology. No thought to cost, availability, access, disease disparity, etc.

Application #	DISC2-13163
Title (as written by the applicant)	iPSC Extracellular Vesicles for Diabetes Therapy
Research Objective (as written by the applicant)	We will derive extracellular vesicles (EV) from induced pluripotent stem cells (iPSC), characterize the content and immunomodulatory activity of EV, and deliver iPSC EV to treat Type-1 diabetes.
Impact (as written by the applicant)	Type 1 diabetes (T1D) is an autoimmune disease and there is no therapy to preserve islet cells. Accomplishment of this project will generate a new therapeutic modality for T1D treatment.
Major Proposed Activities (as written by the applicant)	• EV isolation, characterization and reproducibility • Scaling up EV production in a bioreactor • Analysis of iPSC EV content and identification of the components for EV quality control • Development of a hydrogel delivery platform for EV delivery and prolonged presentation • In vitro assessment of immunomodulatory properties of EV and development of in vitro functional assay • Evaluation of safety and immunomodulatory properties of iPSC EV in vivo in T1D mouse models
Statement of Benefit to California (as written by the applicant)	Type 1 diabetes (T1D) is an autoimmune disease characterized by the destruction of insulin-producing islet cells by the patient's own immune cells. This project aims to develop cell-free immunomodulatory therapeutics based on extracellular vesicles (EV) secreted by induced pluripotent stem cells (iPSCs) to treat T1D. This project will develop a new therapeutic modality for the treatment of T1D and autoimmune diseases, and will benefit our citizens and healthcare in California and beyond.
Funds Requested	$1,354,928
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All Grants Working Group (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	1
Highest	86
Lowest	82
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	6*
(1-84): Not recommended for funding	9

* 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 proposal have the necessary significance and potential for impact?
Yes: 14	• Regulation of autoreactive Immune responses by immunomodulatory extracellular vesicles (EV) could be beneficial to arrest autoimmunity in Type 1 diabetes (T1D). However, the project is at a very early stage where EV donor variability, the need for genetic modification of the donor cells, therapeutic delivery frequency, and in vivo efficacy are still to be tested. • The proposed immunomodulatory EV candidate would provide an unmet need for people with T1D by preventing or slowing the loss of islet cells. • Regulation of autoreactive immune responses by immunomodulatory extracellular vesicles (EV) could be beneficial to arrest autoimmunity in Type 1 diabetes. • Induced Pluripotent Stem Cell (iPSC)-secreted EV could address the limitations of Mesenchymal Stem Cell (MSC)-derived EV: limited proliferation and high variability while maintaining their immunosuppressive potential. • Dynamic iPSC cell culture in bioreactors for cell expansion and EV production are critical for scale-up and clinical application. • Hydrogel-mediated EV delivery could provide sustained EV release after subcutaneous injection and bypass the need for daily injections. • Using iPSC to produce therapeutic extracellular vesicles is very responsive to CIRM's mission. • If successful, this general approach could be useful in many other diseases. • Results of this study may also have wider applications in immunomodulation.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• The proposed project is sound based on the preliminary data and published literature. It is well recognized that EV can be immunomodulatory, but the novelty of this study is the finding that iPSC-derived EV are more effective than EV from MSC. • The investigators present extensive preliminary data which support their proposed study. These include evidence of iPSC EV isolation, gel preparation, and in vitro and in vivo immunomodulation by iPSC EV. • I would like to see more discussion of the pros and cons of using mouse T1D models versus humanized mouse T1D models. • I'd like to explicitly acknowledge the multimodal synergy and phenomenology of this application. Sometimes it is important to try a therapy even if we do not know exactly how it works.
No: 1	• It is not clear where the biomaterial will be implanted to provide localized EV effects where needed (at pancreatic islets), and avert side effects. • Immunogenicity of EV is not described. • Data from bioreactor culture are provided for only up to 3 days (Figure 2). • In vitro release of EV from gels plateaus at day 7 (Figure 4); in vivo release will likely be faster due to gel degradation.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 12	• Optimizing iPSC culture in scalable bioreactors, EV isolation and characterization from multiple iPSC sources, testing their immunomodulatory potential in vitro with both macrophages and T cells, safety in vivo and efficacy in a T1D model are well justified by preliminary experiments. • The study is well planned and should result in a candidate ready for translation to preclinical activities.

	• The proposal is logically designed. The applicant will characterize the EV, optimize the isolation of EV, confirm purity and reproducibility, and then scale up to production in a bioreactor. In parallel the applicant will optimize the hydrogel composition to ensure prolonged presentation of encapsulated EV. The safety profile and immunomodulatory properties of the product will be determined using in vitro and in vivo models. • The proposed alternative approaches to (a) make the EV more disease-specific by crosslinking disease-relevant antigenic peptides to the surface of EV, and (b) study the EV therapy in a humanized mouse model of T1D are overambitious. • Milestone 3 will identify EV composition and attempt to determine the active immunomodulatory components but is not developed further. • The resubmission has addressed the previous reviewers' comments and the submission is greatly improved. • Batch-to-batch variability is problematic in production of EV, but the applicant is aware and has assays to monitor this. • Pitfalls and alternatives are addressed. • Very aggressive timeline for a two-year project.
No: 2	• Preliminary experiments in T1D models do not sufficiently support the proposed studies.
GWG Votes	**Is the proposal feasible?**
Yes: 11	• The proposed milestones and outcomes are achievable within the timelines proposed. • This is a strong and productive applicant with expertise in stem cell biology, bioengineering, regeneration, clinical diabetes, diabetes pathogenesis and drug delivery. However, the applicant has limited experience with EV. • Necessary resources are available to the applicant. • The budget is appropriate.
No: 3	• Given the focus on T1D, a co-investigator (rather than a consultant) with T1D expertise would benefit the proposal. • I am concerned that the manufacturing process for this therapeutic candidate will be too complex to translate to broad clinical application. • The Milestone success criteria are overambitious and not very quantitative.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	• Loss of islet cells is a key feature of type-1 diabetes and improved therapies to address this are urgently needed. The proposed immunomodulatory EV candidate would provide an unmet need for people with T1D across the diverse California population, including underserved racial/ethnic communities where the incidence of diabetes is high. • The proposal includes a helpful description of racial and ethnic disparities in California patients with T1D. • The project will isolate and characterize EV from donors of different race, sex and blood types representative of the diverse Californian (and USA) population.
No: 1	*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.

GWG panelists who gave this application a score of 85 or above were positive about the iPSC EV approach and potential impact among people with Type 1 diabetes. This group noted convincing proof-of-concept data supporting the immunomodulatory effects of iPSC EV, thoughtful and logical project plans, preparation for pitfalls, and potential to expand the iPSC EV approach to other diseases. One panelist described the proposal as very responsive to CIRM's mission and explicitly acknowledged the pragmaticism of developing a therapy even if we do not know exactly how it works. According to this group, the timeline is realistic and the budget is appropriate. Outstanding concerns in the group were the applicant's limited experience with EV, challenges in the production of EV, and practical aspects of translation to the clinic.

Application #	DISC2-13217
Title (as written by the applicant)	An hematopoietic stem cell based approach to treat HIV employing CAR T cells and anti-HIV broadly neutralizing antibodies.
Research Objective (as written by the applicant)	We propose to transduce hematopoietic stem cells (HSC) with vectors that encode chimeric antigen receptors (CAR) targeting HIV and anti-HIV broadly neutralizing antibodies (bnAb).
Impact (as written by the applicant)	Current immunotherapy methods are limited by the rise of escape mutants for single antigens used to develop CAR or bnAb. Our approach solves this issue by generating T cells expressing multiple CAR and B cells secreting multiple bnAb.
Major Proposed Activities (as written by the applicant)	• HSC vector construction and evaluation. • Evaluate CAR T and B cell activity. • Determine whether populations of dual HSC are effective at controlling HIV-associated viremia and reducing the proviral reservoir.
Statement of Benefit to California (as written by the applicant)	HIV is a devastating viral disease that affects over 140,000 Californians and well over a million Americans. Though antiretroviral therapies have significantly reduced the severity and transmissibility of the disease, a cure remains elusive. Anti-HIV drugs must be administered for life, and have been associated with significant toxicity. If the studies proposed here are effective in animal models and then translate to humans, a cure is envisioned.
Funds Requested	$1,143,600
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All Grants Working Grants (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	83
Median	84
Standard Deviation	2
Highest	86
Lowest	80
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 proposal have the necessary significance and potential for impact?
Yes: 13	• Yes. Currently people living with HIV must take medications throughout their lives to maintain viral suppression and stay healthy. The quest for a drug-free HIV remission or a functional cure is of the highest priority to the field. The proposed strategy has the potential to achieve this. Although it would initially be too costly an option for widespread use, it is likely that improvements in efficiencies of production could ultimately make this therapy competitive with the long term costs of anti-retroviral therapy (ART). • CAR T cell therapies for HIV are being explored by multiple groups, but the innovations here are the transduction and transfection of HSC, the addition of constitutive expression of broadly neutralizing antibodies (bNAbs). To date, CAR T cells have not been successful in suppressing HIV or Simian Immunodeficiency Virus (SIV) replication in vivo. The addition of the bNAbs, which is being done here, may be helpful. • The proposal is clearly designed; milestones for progression are well laid out; and experiments are carefully designed with appropriate controls. • Some treatments are available for HIV, but this approach may be an improvement. • The proposed therapy seems highly invasive - I'm not sure whether this will translate to the clinic in light of existing non-invasive therapies. • Yes. CAR plus mAb within a cell therapy could provide durable treatment for HIV.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• The rationale is sound and well-established, based on data that demonstrate that both CAR and bnAb exert antiviral activity in vitro and in vivo. • The preliminary data are convincing, and demonstrate both the applicant's expertise and the study rationale. I have no doubt this applicant can carry out the project. • The transduced HSC are an important innovation of the project, and may contribute to durable suppression of HIV replication in a way that transduction of mature cells would not. • The combination treatment is well-justified by available clinical data.
No: 2	• It is not yet clear whether current CAR T approaches to HIV will be effective. If not, then it is not clear if the applicant's would address the mechanism of failure. • The use of the strategy combines two potential approaches that are immune-based. • Why not just make bnAb secreting cells? • Is this approach targeting the HIV reservoir? • Proof that HSC can express both CAR T and secrete mAbs and have full function is still lacking. • Durability of the treatment could be an issue and should be tested.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 10	• The project will be completed within two years. That is excellent timing for delivering a potentially very important curative therapy. • Milestones and timelines are clearly laid out and feasible. • Yes. From beginning to end this proposal is well thought out. • Much good thought has been put into describing pitfalls and alternative approaches. • Yes, for the most part.
No: 4	• Cell engineering and vector design need to be given more consideration and testing before the applicant moves forward with the proposed studies. • HSC function after gene transfer should be characterized. • The applicant did not completely address comments given in the previous review.
GWG Votes	**Is the proposal feasible?**
Yes: 12	• The timelines and outcomes are clearly laid out and seem feasible. In the previous review, concerns about the impact of the transfections on HSC function were raised. The applicant has addressed these based on the literature in the field. • The applicant team clearly has the necessary expertise in molecular biology and the use of HSC in mouse models of HIV infection. The team is outstanding and synergistic. • The institute has all the necessary resources.

	• I would say that for $900,000 in direct costs, this award is a bargain for CIRM. • Based on the provided data, yes. • The letter of support from the experienced co-investigator seems non-committal.
No: 2	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	• They propose to include HSC from different races and sexes. However, they did not propose to analyze differences based on race or sex. That is a deficiency. It is possible, however, that the study is underpowered to look at this. • HIV disproportionately affects racial and gender minorities in California. If successful, this project would greatly improve their lives.
No: 1	• There is limited information provided that addresses this issue in a meaningful way.

Application #	DISC2-13056
Title (as written by the applicant)	Developing recombinant AAV-based gene therapy for dominant optic atrophy caused by OPA1 mutations
Research Objective (as written by the applicant)	We will develop gene therapy for a major inherited optic nerve disease and test the effectiveness of the treatment by analyzing healthy and patient stem cell-derived mini human retinas.
Impact (as written by the applicant)	The research will use stem cell-based methods to overcome the shortage of human retinal cells and establish disease models, thus allow testing of novel therapeutic treatments for blinding diseases.
Major Proposed Activities (as written by the applicant)	• Analyze cellular features exhibited in patient stem cell-derived retinal neurons by comparison to healthy human retinal neurons • Determine the capacity of patient stem cell-derived retinal neurons to survive under normal and stressed growth conditions • Examine the abnormal forms of the protein in patient's retinal cells, thus identifying the key deficiency of the disease • Study the physiological properties of patient's retinal neurons and determine the visual functional deficits • Construct and produce the gene therapy reagents to deliver the functional proteins to patient's retinal neurons • Test the therapeutic candidate in stem cell derived retinal cells and determine if it can correct the identified disease pathology
Statement of Benefit to California (as written by the applicant)	This proposed research will yield the first therapeutic candidate for treating dominant optic atrophy. Since the defective mutant gene can also cause Parkinson's disease, the study may facilitate a broader research in neurodegenerative diseases, thus benefiting Californians. The research will strengthen the leading position of California in stem cell technology by circumventing the shortage of human retinal cells and accelerating drug discovery for major blinding diseases including glaucoma.
Funds Requested	$1,316,259
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All Grants Working Group (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	2
Highest	83
Lowest	75
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 proposal have the necessary significance and potential for impact?
Yes: 11	• The proposed work could result in a gene therapy approach to alleviate dominant optic atrophy (DOA), a disorder of optic retinal ganglion neurons (RGN). • Even if the development of a DOA gene therapy treatment is unsuccessful, these researchers are already well on the way to making a very sound human organoid model of DOA using retinal oragnoids. This approach is already for the first time allowing investigation of disease mechanisms to be understood, especially with regards to the function of the OPA1 gene, which may act (when mutated) via a haploinsufficiency or dominant-negative genetic mechanism. • Though the outcome of a successful therapy for DOA is not certain, there is some reasonable likelihood of success, and this group has a good vision for how translation would occur. • The proposed candidate is an AAV-based gene therapy for dominant optic atrophy (DOA) which will supplement the reduced levels of OPA1 in patient RGN. The successful development of this AAV vector could provide the first realistic treatment for DOA. • A second candidate, although unfortunately not emphasized by the applicant, is the development of retinal organoids and RGC enrichment to model the effect of patient-derived mutant OPA1 on RGC integrity and function. • Strong disease model for a rare disorder
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 10	• This grant contains strong preliminary data that demonstrates the ability to make CRISPR mutant pluripotent stem cell models of DOA. The preliminary data shows that high quality retinal organoids can be made by this group (including from CRISPR OPA1 mutant induced Pluripotent Stem Cells (iPSC), and these organoids. also contain RGC that have been shown to be functional with patch clamp experiments. There is some very preliminary data to show that mutant organoids have deficiencies in RGN survival. • This group has apparently made a human organoid model for DOA, and also has a plan to develop gene therapies to treat DOA. Therefore, the understanding of DOA disease mechanisms and also the development of gene therapies that might treat this disorder are both enabled by PSC expertise demonstrated by this group. • The project is based on the sound rationale that gene therapy, to supplement the reduced levels of OPA1 in DOA patient RGN, will ameliorate the retinal pathology. Proof of principle comes from successful gene therapy for Leber's Amaurosis. • The model is strong.
No: 1	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 6	• Overall this is a very well designed, disease-focused, and high quality project that may result in an AAV gene therapy to restore OPA1 levels (or swamp out dominant negative action) for the treatment of DOA. • Though a good organoid model of DOA is in place, the understanding of this disorder is still at a preliminary stage, with most of the mitochondrial analysis yet to take place. Thus there is some risk to translational outcomes due to the early stage. However, even if a therapeutic does not come from this work, there is little doubt that a powerful organoid model of DOA will result.

	• Though the model is well developed and excellent, the AAV based gene therapy research plan is less well considered, and would benefit from a considered reworking. • The reduced viability of the mutant OPA1 cells may reduce the effectiveness of the model.
No: 5	• The development of retinal organoids and RGN enrichment to model the effect of patient-derived mutant OPA1 on RGN integrity and function is the strength of this proposal and the team have the necessary expertise to complete these studies. However, this is not the candidate. • It is difficult to assess the candidate itself since the AAV section has no preliminary data and thus the research plan is vague. • The issues of AAV serotype and effect of OPA1 expression in other retinal cells in the organoids in addition to RGN is not addressed. This could be a major problem when given by intravitreal injection. • The AAV gene therapy vector and strategy need to be better motivated and designed.
GWG Votes	**Is the proposal feasible?**
Yes: 10	• The proposed milestones are realistic and outcomes should be met within the proposed timelines. • Yes, no concerns. This is a very qualified team, with a promising new investigator as a Principal Investigator (PI). • This application is from a successful and productive research team with the necessary expertise to perform the studies proposed. They have a history of collaboration. • Excellent team.
No: 1	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 11	• DOA does not exhibit any particular increased incidence based on racial, ethnicity or gender. However this group does have an institutional approval in place to make iPSC from a broad spectrum of patient backgrounds. • The investigators will generate OPA1 mutant iPSC lines from DOA patients with a range of OPA1 mutations and will include all races, ethnicities and sexes. However, the diversity of PSC lines to be used in the proposed study is unclear. • The proposal offers potential benefit to a diverse patient population. • The applicant will attempt to engage underserved populations. • Organizational embrace of Diversity, Equity, and Inclusion (DEI) values.
No: 0	*none*

Application #	DISC2-13150
Title (as written by the applicant)	Novel methods to eliminate cancer stem cells
Research Objective (as written by the applicant)	Our goal is to develop and optimize novel drugs that can attack blood cancer stem cells. These drugs interfere with a target protein, and will prevent relapse of disease.
Impact (as written by the applicant)	By targeting blood cancer stem cells, these compounds can be used to treat and prevent recurrence of cancer in patients. In the future, we will extend this use to other types of cancer.
Major Proposed Activities (as written by the applicant)	• Test several thousand chemical compounds, which are similar to drugs, for their ability to directly stop the protein from carrying out its function • Test a small number of compounds, some of which we have already identified, to see if they interfere with blood cancer stem cells • Analyze the chemistry behind the compounds that work against blood cancer stem cells, and use this knowledge to optimize and build better versions of the compounds for future clinical trials
Statement of Benefit to California (as written by the applicant)	It remains difficult for physicians to treat some forms of acute leukemia, where relapse occurs due to the persistence of leukemic stem cells. The completion of this project will lay the groundwork for future clinical development of drugs targeting these cells via a novel post-transcriptional pathway, which will benefit several thousands of Californians, including many who are from historically underserved populations, who are diagnosed with acute leukemia each year.
Funds Requested	$1,384,347
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All Grants Working Group (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: 81

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	81
Standard Deviation	3
Highest	83
Lowest	75
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 proposal have the necessary significance and potential for impact?
Yes: 11	• It is not entirely clear if small molecules identified in the proposed screen will be useful as a human therapy, as the current state of the research is somewhat preliminary, using leukemia cell lines for the most part, with a good portion of the preliminary data consisting of small animal model experiments. Thus there is some risk that foundational data may not translate from mouse to human. • This application focuses on the identification of small molecule drugs that inhibit IGF2BP3, an RNA binding protein shown to be over expressed in human leukemias, and whose knockdown seems to interfere with the formation of leukemic stem cells in mice. The project falls within CIRM's scope due to the targeting of CSC. • This project might result in the identification of candidate small-molecule drugs that target cancer stem cells (CSC) in leukemia, especially B-acute lymphoblastic leukemia (B-ALL). If successful, this would meet the need of improved therapy for B-ALL, an aggressive leukemia. • The approach appears to be specific to AML and acute lymphoblastic leukemia (ALL) which would be an important advance. • Yes - Acute Myeloid Leukemia (AML) targeting would be great.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 11	• Yes, the rationale is that IGF2BP3 (or related IFG2BP proteins) when over expressed become oncogenic and support leukemia CSC. The hypothesis is that small molecule inhibitors of IFG2BP3 might be therapeutic in human B-ALL. • The preliminary data are fairly sound, based on findings drawn from the study of IGF2BP in human leukemia lines, findings that over-expression of IFG2BP2 occurs in human leukemia clinical samples, and knockdown experiments in cells lines assessed in vitro and in small animal model xenograft experiments. • The preliminary data lack a highly detailed analysis of leukemic stem cells and bulk blast cells that are derived from them, which is typically performed by in-depth flow cytometry. It is surprising not to see extensive flow cytometric analyses in the preliminary data. • In a pilot screen, 1% of compounds tested disrupted RNA binding with IFG2BP3. There is therefore some concern that the screen may have a high noise level, and that many thousands of compounds might have to be validated after an initial large-scale screen. • The finding that IFG2BP3 knockout mice still can perform hematopoiesis suggests that drugs targeting this protein would not cause hematopoietic failure. • There is some concern that arises from the fact that some of the preliminary data come from small animal model leukemia studies. These may or may not translate to humans. • It seems like the target has differential effects on malignant and normal hematopoiesis. • The previously published data for the role of the target in AML is noteworthy. • There is no discussion of currently ongoing attempts to target MLLr-leukemia.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 4	• Yes - provided that the small molecule screen is successful (small molecule inhibitors of IFG2BP are identified and then shown to inhibit B-ALL CSC and their differentiation to blast cells) then a candidate would be in hand for translation. • Overall, this is a proposal to conduct a small molecule pharmacological screen to identify compounds targeting leukemic stem cells. The screen has been conducted already to a degree, with five lead compounds in hand. • The focus on MLL is a plus.
No: 7	• The mouse models may not be applicable to human biology. The target may not have real-world effects in the clinic.

	• The screening assay is elegant, but it is not clear how they will examine the 2,000 hits that are expected. • There are no functional studies with clinical AML specimens, especially those that functionally examine LSC. • The examination of anti-LSC activity uses a cell line without MLL. • The dosing range seems high.
GWG Votes	**Is the proposal feasible?**
Yes: 9	• Yes - based on the preliminary data. • Yes no concerns. • No concerns.
No: 2	• With a 1% positive rate, it will flag a lot of compounds.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 11	• Yes - the grant contains a discussion of the incidence of B-ALL in underserved populations, and a drug to treat B-ALL would benefit these groups.
No: 0	*none*

Application #	DISC2-13191
Title (as written by the applicant)	Key Tools for Spermatogonial Stem Cell Therapy
Research Objective (as written by the applicant)	The two goal of this project are to: (i) purify human spermatogonial stem cells (SSC), and (ii) define a protocol to culture and expand human SSC for future therapeutic applications.
Impact (as written by the applicant)	This proposal directly deals with two bottlenecks holding back SSC therapy to treat infertility: (i) no known SSC-specific markers, and (ii) no reproducible and robust protocol for human SSC culture.
Major Proposed Activities (as written by the applicant)	• Screening candidate human SSC-specific protein markers encoded by genes exhibiting preferentially expression in primitive undifferentiated spermatogonia, based on published gene expression analysis. • Determining the degree of SSC enrichment (using a functional assay) of human testicular subsets purified using SSC markers identified in this study. • Using gene expression analysis to define a "SSC signature" of human SSC. • Using the SSC signature to develop an assay to specifically detect human SSC for future clinical applications. • Leveraging a short-term human SSC culture system developed by the applicant, along with transcriptome data implicating specific signaling pathways, to develop a robust in vitro SSC expansion system. • Determining the molecular fidelity of in vitro cultured human SSC.
Statement of Benefit to California (as written by the applicant)	Approximately 7% of men of reproductive age in California (>1 million men) are infertile. SSC therapy has the potential to provide fertility for many of these cases. One application of SSC therapy is to provide fertility to men rendered infertile by chemotherapy to treat cancer or other conditions. Towards this end, testes biopsies are already being banked by individuals receiving chemotherapy in California.
Funds Requested	$780,180
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All Grants Working Group (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	81
Median	80
Standard Deviation	4
Highest	86
Lowest	70
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	4
(1-84): Not recommended for funding	10

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 proposal have the necessary significance and potential for impact?
Yes: 4	• This approach could eventually lead to the restoration of male fertility by transplantation of male spermatogonial stem cells (SSC). This is a medical need in prepubescent males whose own germ cells have been destroyed by chemo- or radiotherapy treatment for cancer prior to the age at which they can bank sperm samples. In the applicant's approach, SCC would be obtained from pre-pubescent males and then used to restore fertility later in life. • Yes, but there is a fair amount of risk to this proposal, as the applicant has not shown that their sorting technology can be used to purify viable SCC. Furthermore, the proposal lacks a functional assay to determine if the isolated cells can support spermatogenesis. • The project is rather unique and would be the first treatment based on germ cell transplantation. • The preliminary data are very strong.
No: 9	• The panel was unable to understand the overarching impact of this proposal. The impact seemed limited to prepubescent males with leukemia. However, if stem cells were gathered from such individuals, would these be contaminated at low levels with leukemic cells? Wouldn't this be a problem? And would such stem cells from immature males be able to give rise to functional sperm? • This is a unique idea. However, the impact is limited to a subset of infertile males. Cost may also limit benefit to subsets of the patient population. Overall, the proposal addresses a limited niche and is not likely to save money or lives. • How would this technology be used in any other circumstances? How many people would be helped per year? • This is a very "niche" project; the target population is not well described; and adult genetic male infertility is not addressed in this proposal. • The target population is unclear – in which type of cancer can this be used? • Will any biological insight be gained from this proposal, or is this proposal's only deliverable a therapy for infertility? • It seems that 20 known surface markers may be enough to purify stem cells. Why is research needed to find more markers? • No. However, additional data obtained from basic research in this proposal may have wider applications in male infertility.
GWG Votes	**Is the rationale sound?**
Yes: 12	• The rationale of the project is that primitive, undifferentiated SCC might be isolated from biopsies from human prepubescent male testes (which the applicant has access to via a collaborator), and that these might be cultured and expanded for use in human fertility treatments. The applicant proposes to better characterize prepubescent SCC in terms of markers and develop ways to expand them in vitro. • The applicants have built on the application (since its first submission) with preliminary data showing advances in the identification and characterization of cell surface markers of SSC. In addition, single cell gene expression data suggest that there are at least three populations of cells that might be SSC. • If there are no definitive either existing cell surface markers or xenografts, how can the applicant's signature for SSC be validated against a gold standard? Is the applicant relying on expression clustering to create a new gold standard for identifying SSC? • I'm not convinced of this proposal's premise. Is it possible that the sought-after single stem cell doesn't exist? Perhaps the population cycles through different expression profiles and therefore appears to be more than one cell type. Or perhaps two different cell expression types need to co-exist to provide stem cell functionality. • The applicants have answered previous concerns well.

No: 1	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 11	• This project aims to better characterize SSC in terms of their marker expression and, in conjunction, develop a human-to-mouse testes xenograft assay (XGCT) to correlate the expression of markers with the ability of SSC to colonize engrafted mouse testes. However, a second goal, not included in this proposal, would be to expand isolated SSC to provide more cells as a potential source for human fertility restoration. • One weakness of the grant is that the XGCT assay does not assess whether engrafted putative human SCC can go on to produce mature sperm. A future therapy would require both engraftment and the ability of transplanted cells to undergo spermatogenesis, which will not be assayed. • There are some concerns about readiness for translation. The applicant does not propose to assess the ability of isolated and engrafted SSC to support spermatogenesis. Additionally, the proposal does not address whether immature (prepubescent) SSC can be matured to allow spermatogenesis at all. • Some experts on the panel believe that the xenograft assay proposed may be the state of the art. If this is true, the applicant should include discussion of strengths, limitations, and interpretability of the assay. Will it be adequate for assessing the functional potential of different SSC?
No: 2	• Will these stem cells mature to sperm cells? This will be important to test. • Only engraftment is addressed – the applicants do not demonstrate any functionality of the grafts.
GWG Votes	**Is the proposal feasible?**
Yes: 11	• Yes - the proposal aims and milestones can be achieved in a two-year timeframe. • Overall, the panelists believe that the activities in this proposal are technically feasible. • A concern was raised about the viability of cells after the sorting process. This issue should be addressed by providing data showing viability or by comparison to alternative purification techniques.
No: 2	• I am concerned about the timeframe. For example, grafted animals will be harvested at the 6-month timepoint, which will occur in Year 2 of the project. This timing will allow the team ~8 weeks, if everything goes well, to perform the analysis. • Maturation of the SSC is not addressed.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 12	• The proposal is relevant only to males; however, the incidence of infertility in males from various racial and ethnic groups is appreciated by this panel.
No: 1	• It's hard to tell.

Application #	DISC2-13091
Title (as written by the applicant)	Enabling activity-dependent maturation of iPSC-derived neurons using graphene-mediated long-term optical stimulation
Research Objective (as written by the applicant)	We will empower stem cell biologists to generate iPSC-derived neurons more quickly and with enhanced maturation by enabling optical cell stimulation and triggering activity-dependent maturation processes
Impact (as written by the applicant)	Our project will address critical bottlenecks, such as insufficient maturity of iPSC-derived neurons, that limits their utility in age-related neurological disorders that manifest later in life.
Major Proposed Activities (as written by the applicant)	• To fabricate graphene-based substrates for iPSC-derived neurons and human brain cortical organoids in order to use them during subsequent activities for optical cell stimulation • To subject iPSC-derived neurons to repeated patterns of optical stimulation over extended periods of time in order to trigger the electrical activity in neuronal networks • To characterize the changes in functional activity of optically stimulated iPSC-derived neurons that occurred as a result of different optical stimulation protocols • To characterize the impact of the cell activity triggered by optical stimulation on transcriptional and cell population dynamics during activity-dependent maturation • To finalize the validated protocols for light-driven activity-dependent enhanced maturation of iPSC-derived neurons.
Statement of Benefit to California (as written by the applicant)	Neurological disorders are the leading cause of disability and the second leading cause of death. Disease models based on iPSC-neurons allow us to better understand the disease mechanisms and to develop efficacious treatments. However, these neurons often do not exhibit adult-like maturation, limiting the clinical predictiveness of adult disease models. We propose to address this bottleneck by enabling activity-dependent maturation via long-term graphene-based optical stimulation of neurons.
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: 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	81
Median	80
Standard Deviation	2
Highest	85
Lowest	80
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 proposal have the necessary significance and potential for impact?
Yes: 13	• There is an urgent need to improve maturation of iPSC-derived neurons in culture and the development of an optoelectronic graphene platform offers the possibility to address this limitation. • The inability to faithfully recapitulate the adult phenotype can severely limit the potential of iPSC-derived neurons in disease modeling of age-related neurological disorders and drug discovery efforts. Thus, there is a critical need for novel technologies/tools/devices that can aid stem cell biologists in their efforts to rapidly and reproducibly mature and age iPSC-derived neurons. • Proposed biophysical approach not requiring wires and electrodes could mimic the natural environment of the brain during neuron development and training and improve stem cell maturation in functional neurons in a dish. • Technology could empower stem cell biologists to better understand activity-dependent maturation and aging of iPSC-derived neurons, to simplify and accelerate their production, and to generate predictive age-matched disease models based on these neurons. • A very interesting and novel platform. • Novel platform with significant promise in generating novel cell types. • Limited discussion on translation of technology.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 10	• The project is based on the knowledge that neuronal development and maturation are intrinsically activity-dependent and the novel preliminary data on the use of a light-activated graphene substrate. • Proposed stimulation method does not interfere with either structural integrity of a cell or its genetic content, provides uniform and reproducible effects, and offers extended tuning flexibility, while being affordable and user-friendly unlike other methods. • A concern is that the preliminary data appears to have been generated using 605 nm light (which the applicant refers to as green but is in fact orange!) and the proposed study will use 525 nm light for which there appears to be no preliminary data. 525 nm light will have a greater potential for photochemical damage than 605 nm light. • One light wavelength is used in the preliminary data and different wavelength used in the experiments. • No comparison to directly reprogrammed fibroblast that has been shown to preserve the epigenetic make up of the natural age. • Creation of a more realistic model without supporting cells seem not rational.
No: 3	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 9	• Strong preliminary data on the technology and its potential to improve neural differentiation and available platforms and methods. • Strong preliminary data.

	• Strengths include: testing different parameters for stimulation during cell maturation, justification of stimulation frequency per maturation time points, justification of light parameters. • A comparison to state-of-the-art maturation techniques is needed to better characterize the end product. • Many conditions will be tested in parallel, and discussion on expected differences in tested parameters is missing. A table with the experimental conditions to be tested in parallel would have been useful to determine feasibility. • Expected quantitative outcomes are missing.
No: 4	• Significant concerns with photochemical effects on the cells should be investigated. • Support cells may be important to create the best model. • The generation of the graphene platform, the long term analysis of the functional development of neuronal network maturation (Aim 1) and the effect of the platform on transcriptional and cell population dynamics (Aim 2) are well conceived and outcomes are realistic. • A major concern is the naivety of the investigators in cellular photochemical effects. Multiple cellular proteins will absorb at 525nm and the potential for photochemical damage will be dependent upon; a) intensity of light >1mW/mm2 (this is quite high); and b) number of repeated exposures (will lead to accumulation of damage). It is highly likely that light exposure will lead to cellular changes including protein modifications, DNA damage, loss of mitochondrial activity and/or senescence. • A key control which is absent from the study is to compare cells on GraMOS under the proposed optical conditions with cells on GraMOS exposed to normal lab lighting to rule out any chance of photochemical changes. • With the exception of light irradiation concerns potential pitfalls and alternatives are briefly addressed.
GWG Votes	**Is the proposal feasible?**
Yes: 12	• Clear milestones with target quantifiable outcomes. • Excellent resources and appropriate budget. • Many parameters to be tested in parallel, which is a weakness.
No: 1	• This is a productive research team with expertise in many areas of this study. • The lack of expertise of the investigators on cellular photochemical damage is a limitation and the inclusion of a co-investigator or collaborator with this expertise would significantly strengthen the project.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 12	• Applicant appears to embrace DEI values. • The applicant describes potential benefits for underserved communities, but does not address how underserved communities will be involved in this project. • Brief description on how the technology will enable decreasing costs and increasing accessibility to screening platforms and stem cell-derived therapies. • They will generate functional cortical organoids from 10 iPSC cell lines, derived from different human genetic backgrounds, both male and females, to study the impact of long-term externally-initiated neuronal activity on the level and trajectory of maturation. • The investigators will use "10 iPSC cell lines derived from different human genetic backgrounds, both male and female". There is no mention of race or ethnicity.
No: 1	• Not clear if they will use cell types from different ethnic backgrounds.

Application #	DISC2-13035
Title (as written by the applicant)	Reversal of dysregulated myelopoiesis in breast cancers to boost antitumor immunotherapy
Research Objective (as written by the applicant)	A new antiestrogen drug will be developed to stop breast cancer progression by both direct effects on tumor cells and by indirect action on pro-tumorigenic immune cells in the tumor microenvironment.
Impact (as written by the applicant)	A substantial number of patients with localized breast cancer (BC), and essentially all patients with advanced BC, become resistant to current endocrine therapies. A new therapeutic strategy is needed
Major Proposed Activities (as written by the applicant)	• Synthesize sufficient amounts of the 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 the lead drug candidate including estrogen receptor binding and downregulation in vitro and inhibition of human BC progression in preclinical models in vivo. • Assess effects of estrogen on expansion and activation of myeloid-derived suppressor cells in bone marrow specimens from breast cancer patients and antagonist action of the new antiestrogen compound • Assess antitumor action of antiestrogen alone and with immune checkpoint inhibitors in patient-derived BC xenografts in humanized mice, followed by assay of immune cells and cytokines in tissues • Characterize myeloid-derived suppressor cell markers and estrogen receptor expression in anonymous breast cancer specimens including ER-positive and triple-negative BCs
Statement of Benefit to California (as written by the applicant)	Based on data from the California Cancer Registry, there are limited targeted therapeutic options for patients with advanced breast cancer (BC) including triple negative BC (TNBC). This project will develop novel antiestrogens with potent antitumor activity. Furthermore, antiestrogens combined with immunotherapies modify progenitor cell subsets in bone marrow and in the tumor microenvironment to eliminate immunosuppressive cells and thereby more effectively kill BCs to increase patient survival.
Funds Requested	$1,397,000
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	81
Median	80
Standard Deviation	2
Highest	85
Lowest	80
Count	13

(85-100): Exceptional merit and warrants funding, if funds are available	1
(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 proposal have the necessary significance and potential for impact?
Yes: 11	• This application focuses on the development of selective estrogen receptor down-regulator (SERD) drugs, and research is focused on one such candidate. In breast cancer (including triple-negative) myelopoiesis is dysregulated resulting in the production of myeloid cells that secrete tumor-promoting growth factors. The drug seems to inhibit the aberrant myelopoiesis of cells that support breast cancer tumor progression called myeloid-derived suppressive cells (MDSCs). • This proposal hypothesizes that the drug will reverse MDSC activation and expansion in the tumor microenvironment and particularly through modulation of estrogen-responsive MDSCs. Preliminary data generated demonstrates anti-tumor efficacy of the drug in xenografts and mouse models and demonstrated that the drug decreases MDSC numbers and a marker in MDSCs upon estradiol exposure. • This drug might inhibit MDSC cells from functioning in tumor progression, and the drug might be at a stage ready for clinical trials at the conclusion of this research. • The drug acts as an estrogen-receptor (ER) antagonist, or "down-regulator" without acting as a partial agonist. Inhibiting ER is a well-known pharmacological intervention for estrogen-driven breast cancer, but this drug may have some properties involving modulating myelopoiesis by targeting tumor promoting support myeloid cells that distinguish it from other similar compounds already in use. • This treatment approach might also have value for the treatment of triple negative breast cancer (TNBC) as the MDSCs still seem to express estrogen receptor (though TNBC cells do not). This treatment might also sensitize tumors to treatment with immunotherapy. • Applicants suggest that this can be useful in triple-negative breast cancers due to ER+ MDSCs. Actions of SERD compounds do not occur in estrogen receptor knockout mice. • The connection to stem cell research is the modulation of myelopoiesis in breast cancer sufferers due to treatment with this drug that exerts its effect probably in immune and myeloid cells that support breast cancer growth. • Not related to stem cells, gene therapy or regenerative medicine.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 10	• The project is based on a sound rationale. This group has a good understanding of breast cancer (both ER+ and TNBC) and the role that supporting myeloid cells play in the tumor microenvironment. A major scientific rationale is the notion the myeloid cells become incorporated into the breast cancer tumor and support expansion of breast cancer cells. The idea of targeting these support cells is a valid approach. • Large amount of information regarding breast cancer and therapeutic outcomes. A focus on the target and biology of the proposal would be helpful. • Yes, downregulation of ER on MDSCs (and tumor cells) decreases MDSC activation and expansion. Decreased MDSC numbers alleviates suppressive burden on cytotoxic T cells. Combination with checkpoint inhibition can enhance anti-tumor efficacy. The lack of anti-tumor efficacy of checkpoint inhibition in breast cancer is also related to the mutational burden of these cancers, since T cells are reactive to mutated peptides presented in MHC.

	• Yes. The project is based on findings that show that MDSCs, when targeted, (as well as ER+ breast cancer cells) lead to reduced tumor growth. The preliminary data also shows that aggressive breast cancer sufferers have altered (increased) content of MDSCs. • The preliminary data also shows that the candidate drug has promising activity against breast cancer. • Excellent preliminary data. • The use of the drug is hypothesized to perturb aberrant myelopoiesis that occurs in estrogen-driven breast cancer. Specifically, this perturbed myelopoiesis involves the production of myeloid-derived suppressive cells (MDSCs), derived from marrow, but that accumulate in the tumors and these suppress T-cell function and promote tumor survival and further are targetable with the drug. In this fashion, the drug could be considered as a modulator of myelopoiesis. • The goal of targeting ER seems unique. The biology involved, and cellular dynamics to achieve this in vivo is complex, and the applicant has attempted to deconstruct the processes. The role of ER and mechanism of action of the drug is questionable. Unclear why so many models. • Strong data showing the drug seems to suppress ER+ cells in vitro and reduces proliferation, and can compete with estradiol addition to culture compared to fulvestrant, and has induction in growth of ER+ cells and Tam-resistant cells, xenografted in mice. Furthermore, the drug reverses expansion of myeloid cell growth. Unclear how these cells are being affected as evidence that ER+ cells are being targeted is unclear. If not ER+ myeloid cells, then the mechanism of action is unclear beyond effects on STAT3. • The main connection to stem cell research on this grant would be a better understanding of drug-induced modulation of hematopoiesis and impacts on stem cells that participate in differentiation to cells of myeloid lineages. • Other than the potential that myeloid suppressive cells arise from progenitors or HSCs in patients, the stem cell aspect of the applicant is difficult.
No: 1	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 8	• The plan will be to further study the mechanism of the drug and impact on myelopoiesis, and also complete mouse breast cancer xenograft studies which will position this drug for human clinical trials if this research goes as planned. • The milestones include preparing gram quantities of the drug, and also isolating bone marrow stem cells and assessing the impact of the drug on myelopoiesis and also upon tumor progression and growth. • High potential to understand the effect of SERD compounds on MDSCs, including the FDA approved drug. • Will use breast cancer cell lines from African American and Caucasian patients. Will assess downregulation of ER in cell lines from African American women and Caucasian women. • Need to examine dose (where did the starting dose come from?); PD/PK dynamics needs to be assessed.
No: 3	• Good collaboration of clinical and chemistry group to bring a potentially interesting molecule for BC forward. • Mechanistic studies are lacking, and the approaches, although vast, are somewhat wasteful and unclear why methods are being deployed and how they will be used. • Potential pitfalls and alternative approaches are largely not discussed, including if poly-pharmacology matters and if ER is not the direct or only target.
GWG Votes	**Is the proposal feasible?**
Yes: 10	• This group has carefully designed the research plan and milestones into a logical and achievable proposal. This is an excellent and qualified research team. • No concerns regarding feasibility. • This is a lot of work for the time line.
No: 1	• Team is in place and budget seems appropriate.

	• Strong group. However, in vivo model, including organoid systems, are not trivial and there is heavy dependence on other experts.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 11	• Applicant described well the prospects for benefitting underserved communities. • The team expresses a strong embrace of DEI values. • This project would be of special value to African American women who suffer from triple negative breast cancer at increased rates and also suffer from poor outcomes. • May have activity in triple negative breast cancer, which has increased prevalence in African American communities.
No: 0	*none*

Application #	DISC2-13024
Title (as written by the applicant)	Modified RNA-Based Gene Therapy for Cardiac Regeneration Through Cardiomyocyte Proliferation
Research Objective (as written by the applicant)	Efficacious and safe intramyocardial delivery of modified mRNA encoding cell cycle regulators as a gene therapy for cardiac regeneration through resident cardiomyocyte proliferation.
Impact (as written by the applicant)	This project would provide disease-modifying gene therapy for people with heart failure due to loss of cardiac muscle, a leading cause of deaths in the US, using novel modified mRNA delivery.
Major Proposed Activities (as written by the applicant)	• Human iPS-derived cardiomyocytes successfully transduced with modified RNA (modRNA) encoding human cell cycle regulators. • Successful delivery of modRNA encoding cell cycle regulators into mouse hearts • Successful stimulation of human cardiomyocyte division in a dish and adult mouse cardiomyocytes in vivo with modRNA delivery of cell cycle regulators • Efficacy of modRNA delivery of cell cycle regulators on improving ejection fraction in mice with acute myocardial infarction (MI). • Efficacy of modRNA delivery of cell cycle regulators on improving cardiac function in chronic post-MI rats. • Evaluate safety parameters for modRNA delivery of cell cycle regulators in mice and rats.
Statement of Benefit to California (as written by the applicant)	Heart disease is a leading cause of mortality and end-stage heart failure carries a 50% two-year mortality. Few treatments are available and even those do not alter the basis for disease, resulting in ultimate need for heart transplant. We propose gene delivery mediated by modified mRNA, as used in COVID vaccines, to reprogram adult cardiomyocytes transiently into a proliferative state for cardiac regeneration, thereby improving heart function.
Funds Requested	$1,565,784
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	2
Highest	86
Lowest	80
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	1
(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 proposal have the necessary significance and potential for impact?
Yes: 13	• The current treatment options for patients with myocardial infarction to reduce cardiac damage and the subsequent risk of heart failure is limited. The proposed approach focuses on a novel innovative concept which expands treatment mechanisms. • If successful, the proposed approach will likely improve patient care. • The proposed experiments are well designed, and progress from testing disease relevant concepts to the development and evaluation of a potential therapeutic. • This is a highly significant proposal, proposing a novel approach delivering modified RNAs. • Heart failure remains an unmet need for large numbers of patients. The applicants aim to deliver genes to endogenous cardiomyocytes using a technology based on the COVID mRNA vaccine approach. These genes will be expressed for just a few days which should be enough to activate the cell cycle in transfected cells. • The proposed therapeutic will be directed towards endogenous cardiomyocytes but the developmental plan will depend on their testing in iPS-derived cardiomyocytes. Delivery of the gene therapy approach will be accelerated by moving away from viral delivery and instead adopting the same lipid nanoparticle approach used for COVID mRNA vaccines. • The lipid nanoparticle approach to be used has the advantage of being amenable to delivery of multiple genes in one go. This will allow the use of a suite of genes that were previously identified. • If successful, then this approach would certainly address an unmet need. However, there are concerns over off-target effects which have not been addressed and could raise safety concerns. Additional safety studies to explore this would have been helpful.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• The proposed rationale is sound. The rationale is supported by strong preliminary data. The overall concept of inducing resident cardiomyocytes to re-enter a proliferative cell state is well-supported. • The proposal is supported by strong preliminary data. The underlying concept is innovative. • Strong preliminary data supporting the concept. The rationale for moving to modRNA is well-supported and the delivery through lipid nanoparticles is innovative. • The rationale is based on biological observation combined with strong data from previous studies. The first biological observation is that salamanders and zebrafish hearts can regenerate by reactivating the proliferative capacity of the adult fully differentiated cardiomyocytes. The second biological observation relates to mammals, which in general cannot undergo cardiac regeneration. However, its has been observed in mice that for one week after birth, regeneration remains possible, but then the capacity is lost and this loss correlates with a loss of the ability of the cardiomyocytes to re-enter the cell cycle. The applicants reason that by analyzing those genes that regulate re-entry to the cell cycle, they will be able to design a gene therapy approach for re-activation of adult cardiomyocytes. This scientific rationale is strong. • The experiments target mechanisms associated with stem cells. • Mechanistic data are provided. • There are two main concerns. First is safety, overexpressing the selected genes may present a high risk of developing tumors. More preliminary data is required. Secondly, each protein is important at different stages of the cell cycle. How expression is regulated is not defined.

No: 1	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 8	• If successful, the project will provide a novel and highly innovative approach to cardiac cell therapy. • The project's aims and milestones are well developed. The proposed experiments address all major aspects following the identification of the target genes/proteins and mechanisms. The proposed experiments to develop modRNA are well described. The experiments to determine the concentration of modRNA and particles is well-described and designed. The proposed animal experiments are well-described and address critical questions. • The timeline is ambitious, commensurate with the mission of CIRM. • Potential limitations are discuss although alternative approaches are not discussed in great detail. There is a minor concern regarding the efficacy of the proposed modRNAs. This is not discussed in detail. • The safety issues of stimulating cell cycle need to be thoroughly investigated and could create problems. Will the activity of the mRNA be long enough? Re-dosing? • Concerns of safety are not sufficiently addressed, especially as gene expression is still present, although protein levels might decrease. • Overall, the project is well designed and logical. But the in vivo safety studies seeking histological evidence for tumorogenesis will only be conducted in a few animals, and this will only provide an indication of outcome rather than definitive conclusions. No studies are planned to look at the off-target effects of driving cell cycle and this is an additional concern. • The project lacks ambition. The identification and validation of the factors has already be done and the aim now is to change the delivery vehicle from adenovirus to liquid nanoparticles. But the hard drive to translation is lacking.
No: 5	• Safety aspects of the approach need further study. • Higher efficiency in vivo is needed to demonstrate promise.
GWG Votes	**Is the proposal feasible?**
Yes: 12	• The milestones are described in great detail. • The project is feasible and logical. • The team is highly qualified to conduct the proposed studies • The team has high experience in the field. • All required resources are available. • The budget is appropriate. • The proposed timeline is ambitious.
No: 1	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	• Strong organizational commitment to DEI values. • Heart failure after MI represents a sign health burden to the diverse population of CA. • The project is focused on heart failure, which has a high prevalence in underserved communities. • This is an animal study. It addresses differences and increased risk for the respective groups. • The in vitro and in vivo studies do not relate directly to race and ethnicity.
No: 0	*none*

Application #	DISC2-13016
Title (as written by the applicant)	Treatment of Myasthenic Syndrome due to Choline Acetyltransferase Deficiency Using AAV9-mediated Gene Therapy
Research Objective (as written by the applicant)	The AAV9 viral vector will be used to transport the gene encoding the enzyme choline acetyltransferase into a genetically engineered small animal model of the human disease caused by the deficiency of this enzyme.
Impact (as written by the applicant)	Treatment of an incurable disease in infants and potentially amelioration of symptoms of neurodegenerative diseases with deficient cholinergic system, such as Alzheimer and Parkinson disease.
Major Proposed Activities (as written by the applicant)	• Breeding of genetically engineered mice. • Injecting AAV9 virus transporting the choline acetyltransferase gene into mice that are deficient in this enzyme. • Behavioral studies such as Rotarod, metered wheel, grip-strength and electromyography with repetitive nerve stimulation. • Immunohistochemistry analysis of expression of choline acetyltransferase in the central nervous system. • Reverse transcriptase and real time assessment of expression of the gene and the transporting virus in various tissues of the nervous system and peripheral organs. • Histologic analysis of tissues to assess virus induced toxicity.
Statement of Benefit to California (as written by the applicant)	• We found severe weakness and respiratory failure in Native American and Vietnamize infants, which belong to two important ethnic groups of the State of California. • Current treatments for deficiency of choline acetyltransferase are ineffective and the ancillary services required to support patients with this disease are onerous. • We are developing a potentially curative treatment for this disease, which if successful will decrease its financial burden to the State of California.
Funds Requested	$752,102
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All Grants Working Group (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	2
Highest	82
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 proposal have the necessary significance and potential for impact?
Yes: 13	• The disease of interest, a myasthenic syndrome due to choline acetyltransferase (ChAT) deficiency, does represent an unmet medical need. Moreover, this disease is a model for developing the proposed approach for other diseases. • The applicant proposes to use an adeno-associated virus (AAV9) vector carrying a human Choline Acetyltransferase Gene (CHAT) driven by a β-actin promoter to rescue synthesis of Acetylcholine at motor nerve terminals.They will test proof of concept for their therapy in a small animal model of ChAT-related Congenital Myasthenic Syndrome (CMS-ChAT). The study is preclinical in nature and addresses an unmet need in a rare disease. • If successful this treatment could be adapted to other variants of Congenital Myasthenic Syndrome (CMS). Treatment would be administered to humans during infancy and could reestablish swallowing and motor developmental milestones. • The applicant provides encouraging preliminary data and outlines a clear path for translation. • If successful, this would be a game changer.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• This is a gene therapy approach, using an AAAV9 vector to target a functional ChAT gene to neurons. If the project is successful, treatment for this and related diseases will move rapidly to clinical trials. • The vector that is used has tropism for spinal motor neurons - where the ChAT gene is translated - and is thus quite specific. An advantage of the approach is that the genome of the virus and the transported human gene are not integrated into the recipient's genome. The viral transgene persists in the cytoplasm of the cell by adopting an episomal circular conformation. This allows for new, functional ChAT enzymes to be translated and transported by axoplasmic flow to motor synapses. • The use of the human CHAT driven by a β-actin promoter should provide strong, long-term, and ubiquitous central nervous system (CNS) expression. • Some aspects of this therapy are already approved by the Food and Drug Administration (FDA). • The proposal includes compelling preliminary data that support in vivo studies.
No: 2	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 2	*none*
No: 12	• The idea is a basic utilization of gene therapy using a well-studied vector to deliver a missing enzyme. It is difficult to achieve infection of large numbers of cells, which is a general problem with gene therapy approaches. It is not clear how many cells need to be targeted for this approach to be useful. In addition, it is unclear whether native ChAT-producing neurons need to be targeted specifically in order for this approach to be successful. • The preliminary data suggest that early treatment results in an improved motor performance in a model wherein therapy is delivered before disease onset. That said,

	some of the experimental groups showed either no evidence of benefit or evidence of toxicity.
	● In preliminary studies, about half of the treated mice lived until adulthood and showed no apparent weakness. However, the treatment regimens used are not clear. Were the animals pre-treated with AAV-ChAT before loss of ChAT was initiated?
	● The preliminary data indicate potential difficulties for future translation:
	  ● The treatment window using intraventricular injection appears to be very tight;
	  ● Intraperitoneal injection was not effective;
	  ● Results for time of treatment time are confusing;
	  ● Injection routes are not well rationalized; and
	  ● The cell product is not adequately described.
	● The studies using patient-specific iPSC-derived neurons are underdeveloped.
	● A more clinically relevant animal model is needed.

GWG Votes	**Is the proposal feasible?**
Yes: 10	● Overall this is a solid proposal. My concerns include (1) potential irrelevance of preliminary data since mice were treated prior to induction of phenotype and (2) inadequate information on the validation of the system in stem cell-derived neurons. Are these derived from healthy individuals or patients? How many lines will be used, and how will the results be interpreted? ● I believe the milestones are likely to be achieved within the proposed timeline. ● Highly qualified team; expertise is apparent. ● The preliminary studies used a different treatment regimen from the proposed experiments.
No: 4	● It is not possible to tell from this proposal as written. ● Experiments seem to indicate that transgenic ChAT must be expressed before the targeted depletion of the native enzyme to yield benefit. This is not the clinically relevant situation. ● All the necessary resources are available. ● The team is appropriately qualified and staffed. ● Budget is appropriate.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	● The proposal demonstrates awareness of diversity in the patient cohort and inclusion of relevant under-served groups. ● The applicant has learned that this disease is unusually frequent in Native American and Asian groups.
No: 1	*none*

Application #	DISC2-13042
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 1 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	$1,459,018
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	0
Highest	80
Lowest	80
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 proposal have the necessary significance and potential for impact?
Yes: 12	• The product is encapsulated in a polymer based device filled with engineered islet cells combined with two other cell types, and placed under the skin to control insulin dependent diabetes. If the device can be vascularized and evade immune destruction it could help to control insulin dependent diabetes. • The proposed product development will include testing six new hPSC-derived and engineered islets following FDA guidelines into an immunoisolating device for subcutaneous implantation to address donor islet sourcing and need for chronic immunosuppression in beta cell replacement for T1D treatment. • The proposed candidate will be an iPSC-derived beta islet implant. • Development of an encapsulated stem cell-derived islets product with higher functionality than other stem cell-islets could allow beta cell replacement in T1D without immunosuppression with an inexhaustible islet cell source and could be applicable to other cell types for regenerative medicine applications. • The work will progress stepwise through the product development pathway including testing in immune competent mice. • If successful, then this approach would be impactful, but impact is limited by the complexity of the proposed therapeutic. • The product lacks novelty since the device has previously been tested on hESC-derived islets and is therefore focused on translation.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 10	• Encapsulation of the islets will be used to avoid immune rejection in the absence of immunosuppressive drugs. • Co-culture with niche cells may induce a stable programming of beta cells to a functionally mature state, which could produce stem cell-islets with superior functionality than similar products. • A thin film encapsulation device is described and shown to block IgG diffusion, to protect cells from allo-immune rejection, to be biocompatible without a foreign body response and to be compatible with beta islet/niche implants - which retained insulin producing capacity after 42 days. Longer term survival was not explored in the preliminary data. • Device was previously tested with hESC-derived islets, biocompatibility and allograft immunoisolation, though this was done in 2017 and only with insulinoma cells. • Complexity of approach has been addressed in previous work. • The aim is to generate organoids by aggregating hESC/iPS-derived immature beta cells with niche components, including pericytes and endothelial cells. The re-aggregated cluster provides the "engineered islets" for implantation. This is a somewhat complex multi-cell process that may be hard to operationalize in a GMP/clinical setting. • Not clear how the device is different from existing approaches - no comparison provided. • Lack of data showing diabetes reversal by engineered islets to normal human blood glucose levels and of xenograft immunoisolation, though this is proposed in aim 2. • Fig.1B does not include statistical analysis. Also, it is not clear whether these data were previously reported in a peer-reviewed manuscript or are considered preliminary data. • Beta-like cells (BLC) + niche expressing luciferase survive longer in the subcutaneous space of immunodeficient NSG mice than BLC only (Fig. 2A) and when implanted they secrete higher levels of human c-peptide at 6 months than BLC only or intact clusters (not dissociated). However, the figure does not contain sufficient information (number of BLC implanted, blood glucose values of recipient mice).

	• BLC+niche lowers blood glucose of diabetic NSG mice after KC transplantation (Fig. 3) and show stimulated human insulin in blood of recipient mice during glucose tolerance testing. However, the figure only shows average values and statistical considerations are missing. • Fig.4 shows human insulin and not c-peptide levels and it is not specified which time point after BLC transplantation is shown. • Encapsulated BLC + niche showed robust levels of human insulin that persisted through at least 42 days after SubQ transplant into immunodeficient NSG mice, but lacks statistical considerations (Fig. 10).
No: 2	• Preliminary data is lacking statistical analysis (see fig. 3 and 10). • Fig. 2 shows long term survival and production of insulin in NSG mice, but no indication if these levels are adequate. • Although the product did lower glucose in Fig. 3, it is not clear if it lowered enough. Is this dose dependent? • Encapsulation of MIN6 cells in polymer material demonstrates vascularization without too much foreign body response and protection from the immune system which is a strength. Encapsulation of beta-like cells + niche produced insulin for 42 days post implantation in immune competent mice, but hard to interpret this data (no 'n' or stats). • How is this different from other encapsulation devices in this space? • How does this compare to other implanted beta cell methods to control diabetes?
GWG Votes	**Is the proposal well planned and designed?**
Yes: 7	• The project will progress in stages through identification of six candidate commercially valid cell lines to one that can generate beta islet/niche clusters. The chosen cell line will be used to generate islets that will be encapsulated and implanted in diabetic NSG mice, with glucose control being the primary outcome measure, over 3 months. Similar experiments will then be undertaken in immune competent mice. • Concentration of cells not clear, outdated preliminary data regarding stimulation not discussed. • Statistical analyses are missing, no dose response testing.
No: 5	• Experiments assessing dose response or adding multiple devices should be done. • Pitfalls are thoughtfully addressed, but set-backs could be significant in terms of time and cost. • Other nutrients and factors could be added to the device, but increases the complexity significantly. • The proposed work with immunocompetent mouse and human cells may have rejection issues. • Preliminary data is not very supportive of the proposed work. • Feasibility of aim 1.1 is based on published data not on PI's data; the rationale for using donor-derived hPSC lines rather than GMP ESCs is not provided. • In aim 1.2, Glucose-stimulated insulin secretion is not standard (only 2nM and 20mM testing); use of microwell plates for aggregating BLC clusters may not be scalable. • Alternative approach to prevent BLC clumping by incorporating secondary structures into the device to act as physical barriers between the hPSC-derived islets hasn't been tested yet. • In aim 2.2, Diabetic rescue will be defined as achieved if 100% of at least 4 consecutive non-fasting blood glucose measurements are below 250 mg/dL. However, recipients of human islets should be regulated at human normal levels (<100mg/dL); examination of the site of transplant using visual inspection and microscopic examination of the vascular network after intra-vascular dye injection is non-standard (fluorescent lectin injection would be). • In aim 2.2, the applicants suggest that 1000 engineered islets may not be sufficient for diabetes reversal and propose to further optimize the dose but details are missing. Given the availability of preliminary results with 1000 clusters not reversing diabetes, the proposed dose should be increased. The omental fat site is proposed but the applicants haven't performed any feasibility study on this site in mice. • Aim 2.3 with human engineered islets transplanted in immunocompetent B6 mice will require the device to protect against xenorejection which hasn't been proven yet and is unlikely feasible given the results with similar devices.

	• Very nice description of potential pitfalls and alternative strategies. Some of the alternative strategies lack established feasibility. • Very aggressive timeline to develop and test combination product. Aim 2 is very ambitious for a 2-year timeline.
GWG Votes	**Is the proposal feasible?**
Yes: 11	• Year 2 is completely dependent on year 1. If there are no set backs in the creation of cell lines or islet cells, the timeline is achievable. • Immune rejection issues not addressed. • Excellent well-funded team. Additional personnel (post doc, techs) are to be named which could slow the project. • Year 2 completely dependent on year 1, people are not in place to conduct the work. • The project appears feasible, although the nature of the technology, using three cells types together, is overly complex and adds significant risk to the translational plan from a regulatory perspective.
No: 1	• Great team with complementary expertise. • Excellent environment and resources; appropriate budget. • Aim 1 seem reasonable. Aim 2 milestones are very ambitious given the available preliminary data. • Not clear who will provide the devices.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 12	• Thorough description of impact on underserved communities. • Team appears committed to DEI values. • Diabetes is an important disease affecting all populations; this product would eliminate weekly costs and daily testing. • Tools and techniques will take account of different groups. • Very nice and detailed 'Addressing the Needs of Underserved Communities' and 'Diversity, Equity and Inclusion in Research' sections.
No: 0	*none*

Application #	DISC2-13045
Title (as written by the applicant)	Development of small molecules to restore function in neurons from Intellectual Disability Syndromes
Research Objective (as written by the applicant)	We use human induced pluripotent stem cell (iPSC)-derived neurons from patients suffering from Rett Syndrome. We discover molecules that restore function in Rett Syndrome neurons by blocking cellular senescence.
Impact (as written by the applicant)	These novel compounds will treat Rett Syndrome, and potentially any other Intellectual Disability Syndrome where neurons suffer from premature senescence.
Major Proposed Activities (as written by the applicant)	• We will generate small molecules with the ability to enter the brain and block neuronal senescence. We currently have 55 molecules; we will synthesize at least 50 additional analogues. • We will perform activity assays in vivo as well as determine which molecules are most likely viable clinical drugs. • We will determine the mechanism of action of our best molecules to understand how they work to restore function in Rett Syndrome neurons. • We will work with our clinical partner to determine best practices for potential formulation and delivery of molecules, as well as identify appropriate patient populations.
Statement of Benefit to California (as written by the applicant)	The project described here will bring great benefit to families suffering with Rett Syndrome. Our novel small molecules will be translated into drugs that have been shown to ameliorate symptoms of Rett Syndrome in neurons through modeling via human induced pluripotent stem cells. Rett Syndrome strikes 1:10000 live female births, so in a state like California, this means thousands of families are suffering right now, with no treatment options available.
Funds Requested	$1,404,000
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All Grants Working Group (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	3
Highest	84
Lowest	75
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 proposal have the necessary significance and potential for impact?
Yes: 11	• The project area – restoration of normal neuronal function in an animal model of Rett Syndrome – is an important one. Currently there are no curative treatments for Intellectual Disability; if the applicant's hypothesis is correct the outcome of this project could have a broader significance. • Intellectual disability is a huge clinical, financial, and emotional issue worldwide. A drug that would improve treatment for Rett Syndrome or Intellectual Disability in general would be of huge benefit to millions of people. However, the writing and limited detail in this proposal make it difficult to understand what is being proposed. In general, details were lacking in most experiments and preliminary data. • Yes, Rett Syndrome has no cure, and the approach could be valuable for other Intellectual Disability Syndromes. • If successful, this would be an impactful project. • Due to the limited in vivo efficacy data, it is very difficult to predict what the potential for impact might be. • The interpretation of preliminary data is overstated in this proposal. • The applicant extrapolates from Rett Syndrome to other Intellectual Disabilities but does not provide evidence that data obtained from Rett Syndrome neurons will have relevance to other indications. • I suggest that the applicant work closely with a senior colleague on grantsmanship.
No: 1	• The applicant must develop better grantsmanship to convey the significance and potential for impact of this proposal.
GWG Votes	**Is the rationale sound?**
Yes: 5	• The project is based on the applicant's hypothesis that neuronal senescence is a key cause of dendritic branching defects in neurons derived from Rett Syndrome patients. The applicant is working to identify novel small molecules with the capacity to reverse neuronal dysfunction in an animal model of this disease, and potentially expand to additional Intellectual Disabilities. • In preliminary studies, high doses of two of the applicant's small molecules show modest effects on seizure frequency in the animal model. Details on these studies are very limited, and no other in vivo proof-of-concept data is provided. • The applicant's hypothesis is interesting, but not clearly sound. The small molecules identified have not been assayed for inhibitory effects - or, more importantly, reversal – of senescence. • The applicant has not tested compounds identified by others as inhibitors of neuronal senescence. The applicant could provide evidence for their hypothesis if they demonstrate the other, further developed, compounds identified by other research groups show benefit in this model of Rett Syndrome. Of course, a positive result would raise the question of whether new small molecules are needed. • Yes, small molecules provide an interesting therapeutic avenue.
No: 7	• It is not clear that the key issue in Rett Syndrome is neuronal senescence; this hypothesis may not be the best guide for planning therapeutics research. • The applicant should use their Rett Syndrome animal model to test available drugs in this class. • A major issue, as noted by the applicant, is that the team does not have an ideal candidate small molecule. The proposed activities include development and screening to finalize a candidate.

	• The applicant presents preliminary data showing a decrease in seizure number in the animal model with administration of currently available small molecules from their studies. The applicant needs to describe the experimental methods used to generate this data. • The animal model experiments need to be better explained. • The writing in this proposal is difficult to follow.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 5	• Yes. The applicant has identified a candidate small molecule and is now proposing to move towards the clinic by identifying similar small molecules that cross the blood-brain barrier. They then propose to demonstrate proof of concept in an animal model of Rett Syndrome. For future clinical use, the applicant proposes daily dosing in human Rett Syndrome patients using an oral tablet to achieve reduction in seizure activity. • Yes. In their pilot experiment, high-dose treatment with either of two candidate small molecules for two days showed a small reduction in seizure activity. • The in vivo seizure data are difficult to interpret. The applicant provides little information on what is tested in the animal model. The effects are minor, and there is no information on changes in neuronal cytoarchitecture. Furthermore, there is no rationale providing the size of change in seizure activity that would justify proceeding with the project. • I am still concerned about proof of concept because most of the work has been done with cells in a dish or with organoids, and the primary data in the relevant animal model appears to be limited to a modest decrease in seizure frequency. • The applicant reports testing three small molecule candidates in their Rett Syndrome animal model and finding a decrease in seizure activity, but data are only shown for two compounds and the effects are modest. • The question remains as to whether the applicant has tested any of the multiple existing senescence inhibitors in their animal model. In response to this query from our previous review of this proposal, the applicant seems to say that no such studies have been reported. The applicant does not state that they themselves have tested existing small molecule inhibitors of senescence. The applicant should use their Rett Syndrome animal model to test available drugs in this class. • No toxicity has been observed so far; however, this is difficult to interpret as the proposal does not describe the toxicity assays adequately.
No: 7	• The preliminary data do not provide sufficient proof of concept. Figure 11 has some internal contradictions and ambiguities - data for the original lead do not seem to be in the figure, nor is there an explanation or description of the novel analogs. Figure 12 does not demonstrate that high doses of the small molecule candidates decrease seizures, because it is not clear what is being scored as a seizure or what experimental controls were used. • I feel the later milestones are not well justified. If the in vivo experiments were considered successful, why is Milestone 3 (looking for candidates that can cross the blood-brain barrier) proposed? Milestone 4, looking for targets of the small molecule candidate, seems premature as it is unknown that these small molecules will be effective. • The proposed in vivo studies are not adequately explained. For example, one goal is to show the molecules persist in vivo over time, but no experiments are proposed to address this issue. • The grant writing needs to be improved for our panel to adequately judge this proposal.
GWG Votes	**Is the proposal feasible?**
Yes: 11	• Yes. However, there may be a long path to translation as much of the research is focused on assessments of mechanism of action, pharmacokinetics, and early safety. Nonetheless, the search for small molecules that can penetrate the blood brain barrier is necessary for obtaining a candidate that is suitable for translation. • Yes. The generation of some candidate drugs has been accomplished, which seems to make the project feasible. The applicant can do the required work in vitro, and their collaborating laboratory has established a screening program with a Rett Syndrome animal model. That said, the data obtained thus far from the collaborating laboratory is of low quality. • There are many aspects of this project that are well-constructed, and other areas that appear to be enthusiastic over-interpretations of the available data.

	• Yes. Relevant endpoints are suggested - in vitro: restoration of neuronal network activity in Rett Syndrome organoids after 48 hours of treatment; in vivo: reduction of seizure activity in Rett Syndrome transgenic mice after three days of treatment. • There is little description of what it means to rescue Rett Syndrome in the mouse model and what would be considered a sufficient experimental effect size to warrant moving forward. • Yes. However, published data indicate that an existing candidate is able to restore function in Rett Syndrome organoids. • Milestone 3 should be completed before Milestone 2, and Milestone 4 is too premature for this proposal.
No: 1	• I have some feasibility concerns. It is doubtful that a candidate for translation will be ready in two years; the animal model experiments are over-budgeted; no alternative experiments are proposed; and the applicant does not discuss contingency plans if the proposed experiments do not work. • The milestones are logical, but the proposal does not follow the stated milestones. For example, while the overview of Milestone 3 includes molecule half-life, toxicity, and dosing, studies of these characteristics are not included in the text of the proposal.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 12	• Yes, Intellectual Disability Syndromes effect all segments of the population. • Male and female animals will now be used for the in vivo studies. This was an issue in the initial submission. • Yes, this issue is addressed.
No: 0	*none*

Application #	DISC2-13068
Title (as written by the applicant)	Gene therapy vector correcting endoplasmic reticulum stress and GABA uptake defect in myoclonic atonic epilepsy
Research Objective (as written by the applicant)	We will develop a form of gene therapy based on silence-and-replace vectors that silence the mutant SLC6A1 gene but reconstitute GABA transport by expressing a synthetic gene that resists silencing.
Impact (as written by the applicant)	Our work could lead to a treatment for children with mutations in the SLC6A1 gene which cause epilepsy, intellectual disability, motor deficits, attention deficits, hyperactivity, and autism.
Major Proposed Activities (as written by the applicant)	• Use cellular models to develop silence-and-replace expression cassettes that suppress endogenous SLC6A1 expression but rescue GABA transport by expressing a synthetic gene that resists silencing. • Assess the contribution of endoplasmic reticulum (ER) retention of GAT-1 to seizures and behavioral phenotypes in SLC6A1 knockout mice (with no ER stress) or knockin mice (with ER stress). • Demonstrate efficacy of silence-and-replace vectors (AAV-shRNA-SLC6A1) in SLC6A1 S295L knockin mice by assessing seizures (EEG) and relevant behaviors known to be affected by disease. • Combine data from Activities 1 and 3 to identify a clinical lead and set up proof of concept / safety cohorts in mice; define target dose for scale-up and for pivotal toxicology.
Statement of Benefit to California (as written by the applicant)	We propose a gene therapy approach to correct mutations in the SLC6A1 gene, a common cause of autism and myoclonic atonic epilepsy with poor prognosis. Seizures exacerbate developmental delay, and even a moderate relief of symptoms would have a huge impact on the everyday care of a child with this disease. The current treatments are not affordable to many patients especially those from under-served communities. If successful, our strategy could relieve symptoms with a single treatment.
Funds Requested	$1,283,566
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	1
Highest	82
Lowest	80
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 proposal have the necessary significance and potential for impact?
Yes: 12	• Conceptually, this is a very strong proposal. The approach could lead to successes as seen for muscular dystrophy. The project proposes a gene therapy approach to treat children with a genetic form of myoclonic atonic epilepsy. • Myoclonic atonic epilepsy (MAE) is a severe early onset juvenile epilepsy syndrome with very extreme manifestation and no good existing medical treatments. There are some existing treatments, notably the drug Ravicti (phenyl butyrate) and also another gene therapy in development, but these are both of limited effectiveness. • A mutation in the SLC6A1 gene coding for a GABA transporter results in failure to reuptake the GABA neurotransmitter by astrocytes and neurons, which subsequently leads to increased activity of excitatory neurons and therefore seizures. At the molecular level, studies show endoplasmic reticulum stress and reduced transporter levels at the cell surface. • The investigator states that ongoing gene-replacement therapy trials attempt to supplement functional SLC6A1, but additional copies of a functional gene may not be enough to mask the detrimental effects of the mutated gene. The project therefore combines a gene silencing and re-saturation approach to maximize the benefits of the therapy. • The proposed "silence and replace" AAV approach is supported by published work to treat oculopharyngeal muscular dystrophy, which yielded 83% suppression and 63% gene replacement in their disease models. The proposed therapy is expected to meet similar levels of endogenous gene suppression (>80%). • This work may result in a gene therapy approach to alleviate symptoms of MAE. If successful, then candidate AAV vectors and approaches might lead to human trials. • Great potential but very early stage. • Few, if any, effective treatments for this indication; this may prove to be a cure.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 11	• The rationale is based on the finding that SLC6A1 is often detected to be mutated (typically heterozygous) in MAE patients' genomes, leading to haploinsufficiency or dominant-negative genetic mechanisms of disease. • The preliminary data is strong in that this group has done some extensive work with mouse models that harbor SLC6A1 knockouts, and also mice that harbor specific point mutations in SLC6A1 that model some of the human mutations. Overall, these mice have locomotor and seizure characteristics that resemble the human MAE disease. • The preliminary data also shows that GAT1 is mostly expressed in astrocytes (glial cells). • The rationale is sound. The preliminary data supports the expertise of the lab with animal models and indicates that they are capable of performing the proposed studies. • Single cell sequencing of mouse sensory thalamic tissue shows that SLC6A1 is mainly expressed in astrocytes (Figure 6). This is critical information to understand the best strategy to move forward and the investigators will therefore test their AAV in both inhibitory neurons and astrocytes. They will also design constructs with cell-specific expression. • Since 102 risk genes have been implicated in potentially contributing to MAE, there is some concern that gene therapy correction of SLC6A1 may have little or no effect. However, some evidence is presented to show that SLC6A1 may be of key importance.

	• There is no preliminary data to support that the group is capable of producing the proposed vectors within the two-month timeframe they have assigned for this task. This is a significant concern.
No: 1	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 7	• The innovative gene therapy approach consists of two mechanisms: (1) silencing of mutant SLC6A1 alleles combined with (2) introduction of a transgene to make normal GAT1 protein. This is a silence and replace approach. • The idea of knocking down all endogenous SLC6A1 mRNA (whether wild type or mutant), then supplying shRNA-resistant mRNA is a somewhat novel approach. After initial tests of silence and replace vectors in cells, extensive AAV-mediated silence and replace analyses will be conducted in a mouse model to ascertain safety, efficacy, and effects on the alleviation of accumulations of mutant GAT1. • The proposed approach is a valid and very interesting idea with promise of tangible outcomes. However, this proposal is at very early stages and without the tools to initiate the work, is too preliminary to be granted funding. • This is a well-written and interesting proposal, but major concern is feasibility. At present, this is only a great idea. There are no tools in place to execute the project. • The pitfalls associated with transgene mediated expression are not completely considered. It is true that the promoter might be changed if expression is insufficient, but the consideration of too much expression is not considered. • The expression of the transgene SLC6A1 may not be equivalent to wild-type levels of SLC6A1 in normal individuals. This poses some risk. There is some risk that expression from the transgene might be less than wild type levels, or much greater than wild type levels, and the phenotypic consequences of this are unknown. • Perhaps more problematic is the possible heterogeneity of transgene expression among cells themselves based on differing abilities to take up virus or other factors. As AAV vectors can also integrate into DNA, insertion site variability in expression, or changes in copy number of extrachromosomal elements over time may alter the amount of GAT1 expressed, which seems to be quite critical for therapeutic effect. • No preliminary data.
No: 5	• Is there a dose response to the protein? Are there toxicity issues if protein concentrations are too high? Safety issues need to be addressed. Dosing?
GWG Votes	**Is the proposal feasible?**
Yes: 7	• Yes, this is a good team with expertise in GAT1 research, especially in the use of sophisticated allele-specific models of MAE. • Yes, the milestones can be achieved fairly expediently. • The idea is great, but the construct is untested. • Though there is excellent preliminary data on the mouse model in hand, the gene therapy development work is at its beginning, hence there is a fair amount of risk as proof of concept of the silencing-replacement approach for the MAE model is not yet in hand.
No: 5	• Since at present, this is just an idea, there is no way to know if the project is feasible or not. In addition, it is overambitious for a 2-year funding period considering they have not even identified the shRNAs yet. • The entire project is based on testing constructs that have not yet been developed. In the proposed timeline, the applicants have allowed 2 months for this phase of the project. If the applicants do not succeed in this endeavor, no additional/subsequent work will be feasible. • This is further concerning as the animal experiments need to be completed early in year 2 so that the proof of concept studies can be performed later in the year. It seems unlikely that the vector design will be completed early enough to allow this schedule to be achieved. • Construct has not been developed, no preliminary data for a one-time treatment. • The investigators mention that this would be a one-time treatment with long-term mitigation of the epilepsy-related symptoms. Preliminary data to support this would

	however be important as AAV expression can be diminished over time which would lead to the requirement of subsequent interventions. • There are several subpopulations of GABAergic cells in the central nervous system. In epilepsy, only a subset is dysfunctional. How can the gene replacement approach proposed target a specific subpopulation? • The applicants indicate that they intend to perform adult safety, but not neonatal safety. Since treatment in this childhood disease would likely occur at early ages, it would be important to include safety assessment at earlier and more relevant ages. • The investigators state potential pitfalls and alternatives. • They do not provide data showing that differentiation of iPSCs has already been achieved in their laboratory. • They propose an astrocyte-specific promoter to use in the design of the constructs. Is there any data indicating that the expression of this promoter is stable throughout life? How about the other neuron-specific promoters? This should be addressed. • It will be important to ensure that these AAVs and vectors do not induce astrocyte reactivity or neuroinflammation, since astrocytes are one of the targeted populations.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 12	• The applicant does an excellent job of addressing race, ethnicity and sex. Differences between male and female mice are clearly explained and both groups are included in the proposed studies. • Yes. The plan is really just driven by allele frequencies for SLC6A1 defects, which may have some differing frequencies in certain ethnicities. • There are no concerns here. The PI is sensitive to the needs (and possible under-diagnosis for MAE) in underserved populations, but in the end, this treatment will be an option across all groups of individuals who suffer from MAE. • The applicant is working with a patient advocacy group to obtain tissue from as many racial and ethnic groups as possible. • The applicant is also transparent regarding the challenges and the biases inherent in the approach and provides alternatives that could address the current problems. • The proposed therapy will serve the medical needs of all patients, but it is unclear what the cost will be and if underserved communities will be able to afford such gene therapy.
No: 0	*none*

Application #	DISC2-13186
Title (as written by the applicant)	Novel antisense therapy to treat genetic forms of neurodevelopmental disease
Research Objective (as written by the applicant)	We propose to discovery and evaluate antisense (ASO) gene therapy for specific mutations in debilitating or life-threatening neurodevelopmental diseases including epilepsy and autism syndromes.
Impact (as written by the applicant)	The conditions are four specific neurodevelopmental syndromes where mutations are well suited to ASO therapy. The bottlenecks are a current lack of cellular evidence for ASOs to impact disease course.
Major Proposed Activities (as written by the applicant)	• Assemble a cohort of patients and their stem cells for study. • Identify evidence of cellular defects in patient-derived stem cells. • Design ASO therapy for each mutation that can correct the genetic defect. • Assess ASO therapy for effectiveness and safety, and compare with control healthy stem cell lines. • Incorporate data into FDA packages for future clinical trials.
Statement of Benefit to California (as written by the applicant)	Neurodevelopmental disease impacts 1:50 Californians with conditions like severe epilepsy and autism. In prior CIRM-funded efforts, we generated a library of stem cells from patients, and in parallel we identified their genetic mutations. Now the stage is set to test if correction of the genetic mutation through ASO gene therapy can show evidence of disease-modifying activity. Results will set the stage for larger future industry sponsored biopharmaceutical and stem cell trials.
Funds Requested	$1,056,000
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	1
Highest	80
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 proposal have the necessary significance and potential for impact?
Yes: 13	• Finding a way to treat very rare diseases is critical. Such research is understudied and underfunded. I have tremendous enthusiasm for the theme and rationale of this proposal. • De novo mutations are a challenge and a cause of many developmental disorders. • Necessary platform to enable treatment of these rare gain of function diseases. • I really like the collaboration with non-profits. Such collaborations will be key to identifying therapies that would not be pursued by for-profit pharmaceutical companies. • Promising collaboration in an exciting area. • There is potential for an impact, but this will take time. The project is very early stage (no target or validation in place). It is also overambitious, as it proposes to identify a treatment for 4 different mutated genes. • Please briefly describe the FDA N-of-1 pathway. Not all reviewers were familiar with this pathway. • Discuss delivery of antisense oligonucleotides. How will they get through the blood brain barrier? • Discuss safety of antisense oligonucleotides.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 11	• The rationale of using ASOs to treat gain-of-function resulting from small simple mutations is strong. • ASO approach seems rational. • The PI has selected 4 different neurodevelopmental disorders where antisense oligonucleotides (ASOs) are predicted to normalize gene function. As of now, this makes sense but it is just a prediction. • Cell testing is necessary as no animal models are commonly available for in vivo testing. • Please compare ASO with other similar emerging technologies. Are ASOs still the best choice? • Mention the failure of ASOs in Huntington's disease. Why will your project succeed given that HD ASO therapy failed? • Recent data suggest that delivery to cells and tissue targeting using ASO are problematic. • ASOs cannot generally cross the blood-brain barrier, and half-life and sustained levels require invasive multiple procedures - this is not addressed.
No: 2	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 5	• Overall, the plan is good but the lack of focus makes the project superficial and raises feasibility concerns. • In principle yes, but focus on in vitro systems cannot address the underlying reasons of the failed trial. Thus, the approach does not add to an additional understanding of previous challenges using ASO. • There are conflicting statements. In some areas, the applicants state that the compounds being tested are not proposed to be used in clinical trials, however, in other parts of the application clinical relevance is discussed and included in the budget. • It is not clear how the applicant controls for what cells are targeted, how many cells need to be targeted to see an effect, whether off-target effects merge etc... The timing of dosing is also not addressed, do cells need to be targeted during development or is a later time point when the damage already happened still viable?
No: 8	• Safety, dosing, timing and getting past the blood brain barrier need to be addressed. • To make a valuable treatment, consideration of going into patients needs to be undertaken at this stage. • Focus is needed to elaborate the evaluation plan.

	• Consider limiting the target diseases to only those with the most simple mutations. ASOs may not work as well against mutations that involve repeat expansions or large insertions.
	• Why not plan for in vivo animal studies prior to testing the ASOs in humans?
	• There appear to be two distinct project plans that have been editorially mixed together in this proposal. There is a longer plan, that involves human testing and a shorter plan that does not. Different parts of this application are written to different plans, resulting in substantial inconsistencies. Carefully check all application components for consistency, including the descriptions of effort for all personnel. Parts of the application make it clear that there will be no clinical work.
	  ◦ "our study is limited to working with ASOs in preclinical models, so will be tested in human cell lines only." while other parts describe clinical activities (e.g., role descriptions, and "Receive approval and infuse each of 8 novel drugs into patient").
	  ◦ Normally such inconsistencies would drive a low score, but the review committee really liked the premise of the application, so raised the score to encourage resubmission and expecting very substantial and major revisions.

GWG Votes	**Is the proposal feasible?**
Yes: 9	• Environment is very strong. • Letters of support are strong. They may address some of the weaknesses in the proposal (e.g., budget, personnel costs, missing expertise), but they are not explicit (e.g., at a line item level) about exactly what they will provide. • The project is feasible but will not likely yield a new product that moves forward to the clinic in its current form. • Targeting efficiency is not addressed. • The focus on the specific diseases is not clear for example, a recurrent mutation is associated with autism, but it is not clear this is the disease-causing mutation. A more focused and in depth approach of a defined disease would be more informative. • The proposal may be too ambitious and perhaps the proposal would be stronger if it focused on a specific disease. • The core team is strong. Together, they bring very strong genetic and clinical expertise and leadership. However, it is not clear that they already have any of the other project personnel, or whether they will need to be recruited. No other personnel are named. Recruiting a postdoc with the requisite expertise in stem cell biology may not be easy or quick. Computational biologists are also in high demand, so it may not be easy to recruit one. • I recommend a much more detailed timeline, with specific objectives and deliverables and costs provided for each element of the timeline. Which personnel are needed for each deliverable? What is the role of the individuals and entities providing letters of support for each deliverable? How much of the cost of each deliverable is not borne by CIRM, but by other sources (e.g., donated by entities in the letters of support)? • Total personnel costs seem low. I don't see how they can pay all the listed FTEs at typical California salaries and benefits and stay under this limit. • Clarify exactly what role the foundation has. For example, the letter states that "... will select the patient". It seems that the PIs should be doing the patient selection, perhaps advised by the foundation. Describe the patient selection process with enough detail to allow review panel to understand any biases or ethical considerations.
No: 4	• May be difficult to get people hired in time to make the timeline work. • It is uncertain at present since the project is at very early stage. Some preliminary data is provided, but unfortunately there is no real validation of a system in place for this project. For instance, there is no data demonstrating feasibility for the in vitro studies using stem cell-derived neural progenitor cells. If this does not work (issues with differentiation or in vitro phenotype), the whole project is flawed.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	• They seem to have carefully considered diversity and put a lot of effort into meeting CIRM's diversity aims. • Institutional commitment to DEI values is evident. • Track record of inclusive research: "...the 500 cases that were recruited as part of the prior CIRM funded effort were broadly representative of the diverse California population.

	This was evident both in the race, ethnicity and gender reporting during recruitment as well as the inferred ethnicity and gender measured objectively by SNP genotyping of the samples." • This is appropriate.
No: 0	*none*

Application #	DISC2-13206
Title (as written by the applicant)	A new precision medicine based iPSC-derived model to study personalized intestinal fibrosis treatments in pediatric patients with Crohn's disease
Research Objective (as written by the applicant)	We propose to discover a tool that will utilize patient specific iPSC-derived human mini-guts to identify personalized antifibrotic treatments in pediatric Crohn's disease patients
Impact (as written by the applicant)	The major bottleneck in intestinal fibrosis research is the difficulty in obtaining patient-specific biologically relevant cells for in vitro modeling. This iPSC-derived tool would overcome it.
Major Proposed Activities (as written by the applicant)	• Procure cells from pediatric Crohn's disease patients with intestinal fibrosis (Months 0-3) • Reprogram each patient's harvested cells to induced pluripotent stem cells (iPSC) (Months 3-9) • Use high throughput screening with each patient's iPSC-derived cells to find candidate treatments that attenuate each patient's fibrotic response (Months 9-15) • Validation of candidate treatments in corresponding biopsy-derived cells (Months 15-18) • Transcriptomics comparison between matched iPSC-derived cells and biopsy derived cells (Months 18-24)
Statement of Benefit to California (as written by the applicant)	Crohn's disease is a recurring inflammatory disorder that affects the intestine. The prevalence of this disorder in the United States continues to rise each year. There are numerous residents of California with Crohn's disease, 20-30% of whom will require surgery due to intestinal fibrosis. There is no therapy to prevent or treat intestinal fibrosis. The proposed tool would establish a platform that would allow numerous candidate therapies to be tested in a personalized manner.
Funds Requested	$776,340
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All Grants Working Group (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	1
Highest	82
Lowest	80
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 proposal have the necessary significance and potential for impact?
Yes: 11	• This proposal seeks to generate a proof of principle for harnessing induced Pluripotent Stem Cells (iPSC) to generate mesenchymal cells for in vitro testing of potential anti-fibrotic drugs. They key point is that the predictions of the iPSC-derived mesenchymal cell model will be tested against findings of the same studies with mesenchymal cells derived from the same patients. This will allow cross-correlation of the iPSC-model with the use of directly derived mesenchymal cells. • This cross-correlation will be both at phenotypic level (do inhibitors of fibrosis behave the same in both systems?) and at the transcriptomic level. • This is a nice idea, since the use of biopsy-derived mesenchymal cells is impractical in the general clinic, whereas the collection of peripheral blood and subsequent generation of iPSC would be more appealing. • If this approach turns out to work then it would be adaptable to test just about any anti-fibrotic treatment (not just the anti-TGFb molecules under consideration in the present proposal), and could be used with a number of different molecular readouts of fibrosis (not just the specific collagens identified in the present proposal). • Crohn's disease has few treatment options and is poorly understood because the many causal genetic variations create many different phenotypes. This creates additional difficulties to find treatments. A high throughput screening tool could have a significant impact - helping us understand this disease and find treatments.
No: 4	• This is unlikely to be packaged as a kit to have a broad impact. • The aim is to create iPSC from each patient's blood cells and use these to generate mesenchymal cells (MC). The MC will then be used to identify personalized treatments for children with Crohn's disease. • Although the aim is reasonably clear, the application as structured is very difficult to follow for the non-specialist, making it hard to understand the full rationale, feasibility and therefore chances of significant impact. • There is also a lack of clarity on how the applicants intend to achieve a prototype product within the time-frame of the requested funding. • Therefore, in order to be significantly impactful, the proposal would need to be re-written with clarity, to be easily understandable to the non-specialist. Much more attention must be given to demonstrating how a prototype would be ready by the end of the funding period.
GWG Votes	**Is the rationale sound?**
Yes: 12	• Critical assumptions are (1) that there will be a wide variation in response to future therapeutics that will need to be characterized at the individual patient level to avoid futile therapies; (2) that the ex vivo testing will be sufficiently predictive to be clinically useful in this regard. • These assumptions do need further consideration. For example, with luminal inflammation although there is a wide variation in responses of patients, the extent to which this can be predicted using current ex vivo testing or genetic scores is marginal. A predictive score only becomes useful if (1) it is highly predictive (2) there are many treatment choices (3) it is affordable (beyond the scope of present discussion). • The present proposal is very much proof of principle - the proposal uses one particular fibrosis model and one set of putative fibrosis inhibitors (not specified in any great detail) to test whether this approach might allow for individualized response prediction. There is an assumption that there will be other future therapeutics and also, possibly, better fibrosis models that the TGF-b model.

	• Taken together, this is quite a large number of assumptions. Set against this, this is clearly early stage funding designed to support work that does make assumptions - but it would be helpful if at least some of these could be addressed to reduce uncertainty. • I think this is a good start, but the diversity of genetics which cause Crohn's disease will create many complexities in understanding which are the important targets. • I think so. There are indeed a number of potential risks, which the applicant correctly addresses but which it is not possible to mitigate against fully. • The preliminary data are strong and demonstrate the potential success of the tool. • This cell type is important and should be investigated.
No: 3	• The rationale is not clear. Is the outcome meant to be a validated tool, or candidate molecules for further development?
GWG Votes	**Is the proposal well planned and designed?**
Yes: 7	• Clearly well written and justified proposal. Lots of thought has been given to this. The greatest pitfalls are perhaps the risk that iPSC will not recapitulate biopsy-derived cells - but if so then this is useful information and would be a worthy, if disappointing finding. I'm not sure it's possible to mitigate this risk. • WP5 is important to understanding the extent to which the iPSC model is suited to this approach - but felt a bit ectopic - this aspect needs better integration into the overall proposal to explain how and why it will inform future development. • It would also be helpful to spell out specifically what the ultimate goal of this proposal is - what will the tool look like, who might want to use it, and who might have access (i.e., discuss intellectual property rights). • The sample size will allow for limited capture of diversity of response. It may be that a single inhibitor works across all 12 subjects' cells. But some inhibitors may be subject specific. It would be useful if the authors also genotyped the participants since this might be informative in this context, even with just 12 subjects, since the applicant is looking at some very specific pathways. • The risk is that with 12 subjects the applicant will not be able to conclude whether the diversity of responses seen with iPSC cells is accurately captured. I think it is hard to predict or mitigate against this risk - power calculations would be largely speculative and I think using a larger cohort at this stage would risk excessive costs. • The timeline is appropriate; two years to undertake this work is ambitious but appropriate. • Yes. However, this project is too early phase for this award. • Yes. However, the path to the clinic is not clear.
No: 8	• The proposal would benefit from either (1) a plan for how the technology will be translated to other labs, or (2) the development of a kit or company to further develop this tool. • The high throughput screen may be difficult or complicated to interpret. A better read-out would make the proposal more convincing. • The study design lacks clarity in relation to the purpose of each experiment. • The end product needs to be better designed. • The project plan and timeline are compact and reasonable. • Pitfalls are identified and mitigated.
GWG Votes	**Is the proposal feasible?**
Yes: 13	• Yes - I think this is realistic and appropriate. The biggest challenge will be participant recruitment - this is well addressed in the application but should be closely monitored during early stages. • Absolutely - yes. Well planned and mapped. It's all doable - the challenge lies in the assumptions and expectations. • The applicant has good links with clinicians to provide biopsy material. They have good initial data to show feasibility of the key steps involved. • The team has the necessary expertise to carry out the studies and solve any problems that may arise. • The labs are well equipped for these studies. Procurement of tissue and blood samples does not appear to be an issue. • The project as described is feasible. • It is not clear if the technician and post-doctoral fellow are already in place or still need to be hired.

	• The requested budget is a relatively large sum, clearly - but the ambition and scale of the project plus the challenges of working with these technologies justifies the cost. • The budget appears to be appropriate for the proposed studies. • The budget is appropriate.
No: 1	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	• Yes. The tool under development is designed to allow personalized testing of potential interventions. Of course, the ultimate cost of this testing, if this leads to a commercially available tool, might be beyond the means of those without good healthcare access, but this is a societal problem. • I was impressed by the level of thought and input that had been given to this question and the response provided by the applicants. I think this is really well covered and the case well made. • The applicant plans to develop cell banks from several different ethnic groups to test their system. • Cell lines representing different communities will be sampled.
No: 1	*none*

Application #	DISC2-13122
Title (as written by the applicant)	Drug Development of Inhibitors of Inflammation Using Human iPSC-Derived Microglia (hiMG)
Research Objective (as written by the applicant)	We will screen for modifiers of the response to misfolded αSyn and Aβ, and their cognate antibodies. Development of drugs to combat this inflammation is important in neurodegenerative diseases.
Impact (as written by the applicant)	Inhibiting the immune response to minimize NLRP3 inflammasome activation may prevent the neurotoxic effect of activated microglia, and attenuate disease progression in neurodegenerative diseases.
Major Proposed Activities (as written by the applicant)	• High-throughput Screening: Screen for hit-to-lead compounds that inhibit immune activation triggered by misfolded proteins, monitored by (1) IL-1β reporter line and by (2) ELISA (month 1 – month 6). • Efficacy Evaluation of Hits: Evaluate candidate therapeutics in hiMG using misfolded proteins in the presence and absence of their cognate antibodies (month 6 – month 18). • Drug Optimization (month 18 – month 24). • Further Develop and Complete a Target Product Profile (month 21 – month 24).
Statement of Benefit to California (as written by the applicant)	This proposal will benefit citizens of California by developing new treatments for Alzheimer's disease and Parkinson's disease based on new anti-inflammatory pathways studied in the innate immune cells of the human brain, represented by hiPSC-derived microglia. These diseases are very prevalent in California, and cause both personal tragedy to families and undue economic burden. Developing a new therapy for these conditions will alleviate this suffering while benefitting the California economy.
Funds Requested	$1,648,670
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	85
Lowest	75
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	1
(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 proposal have the necessary significance and potential for impact?

Yes: 11	• Targeting neuroinflammation in Alzheimer's disease (AD) and other neurodegenerative diseases is a well-established and reasonable approach to therapeutics. The strength here is the use of the microglial screening platform used to test for compounds that interrupt the inflammasome pathway.
	• The project proposes to screen for small molecule compounds that will inhibit or reduce neuroinflammation associated with misfolded proteins (e.g. alpha-synuclein and amyloid-beta). These compounds would have the potential to treat a variety of neurological disorders that currently lack effective therapies.
	• AD is an important disease, as are other neurodegenerative diseases. Finding drugs for these diseases is very significant and important. This proposal aims to target something other than amyloid, which is very welcome in this field.
	• Huge issue and no effective solutions at this point.
	• The proposal indicates an intent to evaluate the compounds in mouse models of neurological disease in future work.
	• The project is early stage screening and in vitro evaluation of compounds that inhibit inflammasome activation in iPSC-microglia. The path to translation (a long process yet) is not discussed.
	• Concerns relate to the lack of discussion of compounds already either in trial or even in use that may target the same or related pathways. Why are these compounds better? What is the measure that would suggest that a "hit" in the current testing paradigm meets a level that it should be developed into a drug?
	• Please place this project in the context of other related research in your and other labs:
	  ◦ How does the proposed research on this drug distinguish itself?
	  ◦ Is the proposed research the logical next step in research for this drug, or should other studies be done first (e.g., a thorough investigation of the drug itself).
	  ◦ Is anyone studying the plant extract? E.g., short review of recent publications
	  ◦ Is anyone studying the drug? Why not just focus on the drug? Why the need to search for other similar compounds?
	  ◦ Why not screen the ReFRAME library rather than focus on phenols? If such screening is being done in parallel by other funded research, consider mentioning why this project should also be funded.
	  ◦ Why not screen an even larger compound library?
	  ◦ Why focus on plant-derived compounds? Wouldn't there be a lot of synthetic compounds similar to the drug?
	  ◦ How many phenolic compounds are there in your library? At least 200, so how many more are you not screening? What fraction of compounds are similar enough to the drug for there to be reason to believe they share its property? Can you provide a couple of names of these 200 compounds to give reviewers a chance to evaluate the claim that these are similar to the drug?
	• Don't assume reviewers will read the cited references. Any key information should be in the proposal.

No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 5	• The rationale is sound, in that they will screen novel compounds for their ability to inhibit the release of IL-1β from microglia, and activate the Nrf2 pathway is a strength of this proposal. • The premise of using iPSC-microglia in screening for drugs that inhibit inflammasome activation is strong. • The efficacy of inflammasome inhibition in treating neurodegenerative diseases has not been established, although it is reasonable to investigate. • Preliminary data establish generation of iPSC-MG and demonstrate induction of inflammatory responses in the cells by misfolded proteins.

	• Preliminary data demonstrate that the drug can inhibit inflammasome activation in iPSC-MG via NRF2 activation. These data support the use of the iPSC-MG model in drug screening for anti-inflammatory compounds. • The expected 15% hit rate seems high. Please provide more justification for this expectation. For context, perhaps provide the hit rate from several other similar efforts for other drugs/diseases. • Explain why no anti-inflammatory drug is currently being used as standard of care for Alzheimer's disease. Surely a drug of this class would have been noticed as having a protective effect by now – if there was such a protective effect. • There are numerous publications in PubMed showing the drug is effective on other cell types and using other mechanisms of action than that described in this proposal. Why should we consider your described mechanism and target as more believable than these other published mechanisms and tissue targets? • If the drug works through multiple mechanisms on multiple tissue types, then your IL-1β assay may only be partially relevant. • If the drug affects many tissue types, why should its study be emphasized more than any other anti-inflammatory? • A weakness is that they do not really emphasize further development of the drug, which seems to be the lead compound here. They also do not discuss screening of FDA approved drug libraries, which could accelerate the identification of a therapeutic compound for trial.
No: 6	• Why is this better than other anti-inflammatory compounds? The screening tool is well developed. What compounds? Why these? Should test some currently used drugs to check the screening tool. • If already have this lead compound, why not move forward with it? • Not sure why the lead compound is not pursued. • Selection criteria of compounds are not clear.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 8	• The planning is sound for a drug discovery platform. • Not well integrated into existing data – how is this research/compounds adding to the existing therapies. • What is the definition of a compound being better than the drug? Discussion of comparable criteria is not clear. • Limited attention to activity. • One reviewer wanted an in vivo aim, as further validation of the utility of the best hits. However, another reviewer would have balked at such an aim, as it would imply funding an aim completely dependent on a previous successful hit ("linear aims") which might not happen. Therefore, consider providing a plan for in vivo studies, either in the proposal or as a future direction. And justify this plan based on cost and timeline considerations. • Why no controls? Use some drugs without anti-inflammatory properties as negative controls and test other cell types besides microglia – these should not respond if the drug is specific to microglia. Test known anti-inflammatory drugs to see if they also elicit IL-1β. • Make sure math is consistent (and correct & clear) throughout the proposal. The numbers in the aims were inconsistent with the numbers/math in the pitfalls. • Avoid acronyms wherever possible. Please use standard acronyms that would be recognized by reviewers from a wide range of specialties, and declare them each time they are used in distinct application component. E.g. hiMG = Huntington Internal Medicine Group iADRS = not defined in the manuscript (at least not in the section I read first) SAR = search and rescue; not defined the first time it is used.
No: 3	• Lead compound optimization considers in vitro pharmacokinetics and plasma stability, as well as early stage predictions of BBB penetrance. • The screening approach is detailed and well-designed. The use of IL-1β secretion in the presence of misfolded proteins is very "screenable". Primary and secondary measures of IL-1β are provided. • Investigation of the effects of screen hits on microglia includes relevant markers to the mechanism of inflammasome inhibition.

	• The project proposes to screen 200 plant-derived compounds with an anticipated hit rate of 25%. If they are not successful they propose to screen larger, less focused compound libraries. • The project is very early stage discovery (hit-to-lead). It will not achieve a candidate ready to advance to translation. If successful, the project will identify leads that can be investigated for specific applications in inhibiting neuroinflammation. • The assessment of microglia phenotypes by the compounds is very cursory. • The project does not benchmark hits to known inhibitors of the inflammasome. • The lack of evaluation in an in vivo model of neuroinflammation is a weakness. • The project plan does not consider specificity or off-target effects of the compounds.
GWG Votes	**Is the proposal feasible?**
Yes: 10	• The proposal is feasible as written. • Progression is excellent. • Milestones are carefully constructed and quantitative. • There is a strong likelihood of success of the milestones. • The team is highly skilled in the iPSC-MG model and in drug screening applications. • Strong team. • Strong environment. • The team would benefit from expertise in a neurodegenerative application to accelerate translation for a specific disorder. • A better explanation of why the need to look for compounds other than the drug would be helpful. Also some indication of what level of anti-inflammasome activity signifies a "hit". • Minor issue: It would be useful to be more specific about what "developed" means in the sentence "having developed 4 FDA-approved drugs based on …". This approved drug has a long history. A quick online search was insufficient to judge whether the applicant's previous work with the approved drug was similar to the work proposed here for the new drug. • It isn't clear that the proposed work involves figuring out a mechanism of action, as the mechanism of action of the proposed drug is already claimed to be known.
No: 1	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 10	• The commitment to DEI values of the institution is evident. • The screen uses cells from various ethnic backgrounds. The treatment will be beneficial to all groups. • The investigators intend to use iPSC lines from donors of different races and sex, but specifics on the lines are not provided. • Neurodegenerative diseases affect all groups in California's population. The proposal suggests a particular burden on women and Latino communities. • Diversity statement is currently a bit effusive. The main focus should be on the diversity of the cell lines and iPSCs to be used. It is not currently clear these are adequately diverse. • In theory, though how this project will do so remains in doubt.
No: 1	• Though the PI states that this project addresses the diverse population on page 7: "Here we are using hiPSCs that will be obtained from a variety of sources, representing the underserved racial and ethnic communities, such as Latinos and Black, and both genders as found in California", this issue is not mentioned again. • There is no indication of from whom the initial iPSCs will be derived from, and the publication most referenced states that these cells were obtained from national banks. It would certainly be interesting to see if iMG from different genders and racial backgrounds respond differently in this assay, but that is not mentioned either in the preliminary data or in the proposal. So where are these iPS cells coming from? • Not clear why iPSC cell collection does not represent a diverse population.

Application #	DISC2-13220
Title (as written by the applicant)	Bioengineering human stem cell-derived beta cell organoids to monitor cell health in real time to improve therapeutic outcomes in patients
Research Objective (as written by the applicant)	We will generate nanoprobe-containing stem cell-derived human beta cells that can be monitored in real time in response to inflammatory stress upon transplantation in patients with type 1 diabetes.
Impact (as written by the applicant)	Our product will replace donor islets for cell replacement therapy in patients with type 1 diabetes, and will provide a readout of cell survival and an opportunity for therapeutic intervention.
Major Proposed Activities (as written by the applicant)	• Test beta cell organoids with nanosensors to secrete insulin in response to elevated glucose levels, and test similar functions in animal models of diabetes • Test the ability of beta cell organoids with nanosensors to emit a measurable signal in response to increased cytokines in the environment in culture and after transplantation in small animal models • Modify the response of nanosensor-containing beta cell organoids to cytokines using supportive niche cues
Statement of Benefit to California (as written by the applicant)	The American Diabetes Association states that California, with the highest number of patients with diabetes in the country, also has the highest cost at $39.47 billion. A large proportion of these patients are insulin-dependent and are potential candidates for islet replacement therapy. Developing technologies that can improve transplantation outcomes in patients directly affects long-term quality of life. All staff are CA residents, with a long history of collaboration with a local academic institution.
Funds Requested	$1,198,550
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All Grants Working Group (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	81
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 proposal have the necessary significance and potential for impact?
Yes: 11	• A cell therapy candidate that improves control of glucose levels in type 1 diabetes patients would impact the unmet medical need of improving outcomes for T1D patients. • Intriguing technology and could be a useful tool with applications in several places. • The technology results in a homing beacon to identify endogenous RNA species without pre-amplification to monitor local inflammation in transplanted stem cell-islets and inform on therapeutic treatment (if localized delivery strategies are available).The design of this early stage translational plan is logical, leveraging in vitro optimization and in vivo evaluation in relevant murine models of T1D. • Technologies to monitor cell grafts in vivo have significant potential to improve many different cell therapies. • The sensors developed here have strong potential as a platform technology to monitor cell and tissue therapies in situ. This is a major roadblock for development and implementation of stem cell-based therapies. • If successful, the project would presumably transition to larger animal models en route to human trials. • Inclusion of stem cell-islet pro-survival factors such as those derived from parathyroid tissues, if those can be effectively identified. • Transplantation in more clinically-relevant and less invasive sites is a strength, though proposed work will be done in the kidney capsule. • Recently awarded grant will help technology development for hypoxia in vivo monitoring and leverage research proposed here. • A novel technique is proposed that may make it possible to track that mass and inflammation of transplanted beta like cells derived from stem cells. The investigators are outstanding. The weakness is that not enough data have been generated to show how well the methods might work. • Strategies to improve viability and engraftment of beta cells and pancreatic organoids would overcome a roadblock for using these to treat T1D. • The depth of penetration of signals is limited. This isn't much of an issue in subcutaneous or kidney capsule transplantation in a mouse. However, organoids transplanted into the human liver or other sites are unlikely to be detected with the technology described here. The proposal does not adequately address this challenge of translating from small animal to human treatment. • Use of cadaveric parathyroid tissue in a cell-based therapy has translational challenges including access, safety testing, and immune rejection. • The proposed development of a product that includes: stem cell-derived islet organoids with inflammation sensors, pro-survival factors derived from investigating the beneficial effects of parathyroid tissue co-culture, and different transplant sites is overambitious at this early stage and lacks focus. • The capability to intervene in case of detected local inflammation in grafts relies on the availability of treatments for localized immunomodulation.
No: 1	• Likely low clinical relevance.
GWG Votes	**Is the rationale sound?**
Yes: 11	• The premise of using stem cell-derived beta cells and pancreatic organoids in treating T1D is strong. The concept of parathyroid conditioning of the cells is innovative and seems sound. • Nanoparticle sensors are a technology well-suited to monitoring molecular features in vivo where depth of penetration is not a major concern. • Monitoring of nanoparticles as a way to probe implant health is innovative and sound. • Preliminary data demonstrate expertise in generating the stem cells and organoids used in this study. They also demonstrate that the nanoparticles do not negatively impact differentiation. • Preliminary data establish the ability to detect nanoprobes in vivo.

	• The rationale makes sense. • A link between the nanoparticle and transplant outcome has not been established. This is critical for success of the project. • The optical technique is not easily scalable.
No: 1	• Preliminary data show feasibility of each separate approach but not of the combined product. • Demonstrated gold particle incorporation is not impairing beta cell differentiation but detection by the system is not shown. • Most data have been generated with a different cell source. • Figure 6 lacks OFF control for determining sensitivity of detection.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 7	• In deep tissues there may be a considerable amount of signal loss. Is there a plan for this?
No: 5	• Sensor development and design is very well-considered based on prior work by this team. • The use of complementary in vitro models to optimize the technology then disease relevant in vivo models to assess performance is a strength. • The study uses relevant models and experiments are well-designed with key details provided and clear controls. • The team proposes ways to modulate immune "activation" of the transplant via cytokine pretreatment as a control. • The only serious weakness is that not enough data have been generated to convince the reviewers that the data obtained from the proposed experiments will be of great value. • In vivo studies depend on the capability to develop the inflammatory nanoprobes and on the capability to detect nanoprobes incorporated in organoids. • The lack of consideration of signal loss and detection in deep tissues in humans is a weakness in translation. • A weakness of the design is the lack of a clear linkage between the nanoparticle and outcome. Experiments do not appear to be designed to establish that this measure is a proxy for transplant health. • Activity 3 is unfocused, using various recombinant factors and cadaveric parathyroid gland tissue to protect against inflammation, but the specific nature of this inflammation is not clear nor the mode of action of these factors/tissues. It isn't clear the pre-stimulation of the implant with cytokines is an appropriate model for the stresses that lead to low implant engraftment and survival. • Parathyroid factors' beneficial effects haven't been determined yet so activity 3 seems overambitious. • The key pitfall not addressed is what to do if the signals are not predictive of transplant function. • Probes are irreversible. • Success of proposed work depends on capability to successfully adopt technologies from collaborators.
GWG Votes	**Is the proposal feasible?**
Yes: 9	• I am excited about the technology and hope the work can continue. • The milestones are very quantitative and appropriate for the focus of the project. • The team has expertise in nanoparticle design, stem cell differentiation, and the diabetic mouse model proposed. • The co-founders of the company appear engaged in the company and the staff at the company appears to be in place. • The team might benefit from consultants with expertise in inflammation to align sensor design with transplant outcome, and how to intervene upon sensing inflammation. • The team has access to necessary facilities. • Aims seem overambitious.
No: 3	• Very detailed milestones and quantitative outcomes to determine success. • The PI has extensive experience in product development, commercialization, and managing multidisciplinary science and engineering teams. • Aggressive timeline to get all of the testing completed.

GWG Votes	Does the project serve the needs of underserved communities?
Yes: 12	• T1D disproportionately affects underserved racial/ethnic communities so improving cell-based therapies to treat this disease would serve a major unmet need in this regard. • The commitment of the company to diversity is outstanding. • A complicated question because of the demographics of people with T1D. • The project proposes to use iPSC lines derived form individuals from diverse backgrounds. • The animal studies do not consider sex as a biological variable. • Plan to include iPS cell lines that are generated from women, people of color, and people with diverse ethnic and genetic backgrounds. • Mention of Spanish-speaking California residents affected by T1D.
No: 0	*none*

Application #	DISC2-13023
Title (as written by the applicant)	AI-aided rapid automated functional assessment for iPSC treatment of spinal cord injury
Research Objective (as written by the applicant)	An artificial-intelligence (AI) tool for testing and documenting the therapeutic benefits and safety of pluripotent stem cell transplants for spinal cord injury (SCI).
Impact (as written by the applicant)	The AI-assisted tool will replace costly and time-consuming manual determinations of benefit in preclinical animal models, greatly accelerating the validation of SCI therapies for use in humans.
Major Proposed Activities (as written by the applicant)	• Adapt and optimize AI-assisted image analysis algorithms for quantifying body and limb movements in rats. • Determine if AI-assisted movement analysis provides more reliable measures stem cell transplant effects in spinal cord injured rats, in contrast to manually scored behaviors by human observers. • Develop enhanced versions of AI-assisted movement analysis that provide much greater resolution of movement in individual limbs, paws, ears, whiskers, tail and even individual digits on each paw. • Make the computational AI-algorithms freely available and accessible through web-based tools that any researcher can use with ease.
Statement of Benefit to California (as written by the applicant)	The functional validation of stem cell therapies for spinal cord injury in animal models is extraordinarily costly and time-consuming due to the current scoring of behavior by human observers who watch and manually tally individual movement features as rats perform a task. The successful development of unbiased AI-assisted motion analysis for rats with spinal injury will eliminate this biased assessment with agnostic and accurate computer-based measures at a tiny fraction of the time and cost.
Funds Requested	$784,954
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	4
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 proposal have the necessary significance and potential for impact?
Yes: 9	• The aim is to increase throughput and reduce costs of neurological assessments in animal models. • If it were possible to have a reliable automated system to provide quantitative information on complex behaviors, this could greatly speed up analysis of cell therapeutics for neurological trauma. • Addresses the bottleneck of the time consuming testing metrics that rely on the human observation and scoring of artificially stereotyped behaviors. Another test uses the same behaviors and from this point of view, this project is not a progression. • The applicant proposes that potentially novel behavioral aspects will be revealed but this claim is not underscored by preliminary data. The program is developed on the basis of assays and readouts that are already established and are inherently biased. It is not clear how new, and as of yet, unknown behavioral SCI relevant aspects can be discovered. • To address the urgent need more effectively, the applicants could have discussed whether the approach has generated advantages in the epilepsy field. Is the approach generally used and accepted, and has it saved money and time? • Was the dissemination strategy of the program in the epilepsy field successful? Considering that these data are used as a proof of concept baseline, it might be more useful to develop the aspect of reproducibility, dissemination and FDA acceptance in the epilepsy space rather than approaching a different injury with a very complex behavioral profile.
No: 5	• The system has been developed for measurements in mice, the goal here is to implement the system in rats. It sounds incremental. It would be helpful to understand how the system implemented in mice has helped the scientific community. • I do not think the significance is high. This automated system could be very helpful for performing behavior assessments but it may not impact an unmet medical need. • The technique is not tested robustly for a clinical/translational application.
GWG Votes	**Is the rationale sound?**
Yes: 8	• An automated system for functional assessment of potential treatments for spinal cord injury in rats is desirable.
No: 6	• The big question is whether this is a realistically achievable goal. The variability in recovery profiles between different animals is large, even in the highly artificial laboratory situation of trying to decrease variability between injuries. • Recovery is nuanced in animal models. The differences in recovery may differ in different aspects of movement between animals. These differences are captured by using the combination of BBB scoring, Catwalk analysis and analysis of neuropathic pain responses (at a minimum). • The scoring of recovery is much more complex and nuanced than is the case for analyzing the much simpler problem of seizure behavior (which itself is more complex than indicated, with a need to grade different kinds of seizure behaviors). • No SCI data, it seems a bit premature. A pilot study to test whether the approach can distinguish naive from injured would have helped, especially in light of collaborator who has an iPSC approach in SCI using classical approaches and 5 behavioral tests are used as comparative baseline.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 10	• Making the software freely available is a strength. • The proposal is well designed. • The method has been successfully used for detecting and quantifying the sensorimotor features in epileptic mice and can identify mice treated with anti-epileptic drug versus

	controls but this behavior is not relevant for SCI. Sensitivity of the tests for far less obvious changes in SCI is not clear. ● Yes, to a point. But there really is no testing of the hypothesis that this performs as well as the trained observer in respect to the variability in recovery between animals, or the potential subtleties between different cell preparations. ● In the context of SCI, variability is high and informative. An approach that focuses on the most apparent changes might eliminate data of animals that show slight benefits in some domains but not others. ● Although it would be wonderful if the idealized goals of the proposal can be achieved, right now there is an absence of evidence that this is achievable.
No: 4	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 12	● Overall, the approach seem feasible although the aims depend on each other. For example, Aim 3 to enhance capability seems obsolete if Aim 2 does not work. ● If this approach can work, then this team has an excellent chance of making that happen. That said, the information presented is not convincing that the goals of the project can be achieved in a useful manner. ● It is not clear at what point it would be decided that the approach is not working – how many optimizations can be made? ● Would the approach be useful to studies in the next larger animal model that is usually used for validation?
No: 2	● There is a lot of work to be done from the preliminary data to assessing the subtle details of various disease models. There is much variability between animals, so the technology would need to be precise to see small differences or robust enough to understand an improvement in one parameter is equal to an improvement in a different parameter.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	● Likely to offer benefit should it be implemented and successful in translational research. ● SCI affects all communities. ● The institution embraces DEI values. ● Yes, indirectly. A more affordable and faster approach to test efficiency would allow for testing more samples and would allow inclusion of more diverse preclinical cohort related to sex, age, strain, etc..
No: 1	*none*

Application #	DISC2-13120
Title (as written by the applicant)	GlyTR1-CAR T cells targeting abnormal N-glycans for the treatment of Glioblastoma
Research Objective (as written by the applicant)	Develop genetically modified chimeric antigen receptor T cells to kill glioblastoma (brain cancer) cells by targeting a previously un-targetable tumor associated carbohydrate antigen.
Impact (as written by the applicant)	Glioblastoma brain cancer has an abysmal 28% two-year survival rate. There is a great need for new therapies. CAR-T cells are the most potent cancer immunotherapy and provide a potential new therapy.
Major Proposed Activities (as written by the applicant)	• Engineer and optimize a genetically modified chimeric antigen receptor T cell that targets a tumor associated carbohydrate antigen with high sensitivity and specificity. • Confirm the ability of the engineered CAR-T cells to kill glioblastoma cancer cells. • Assess the risk of toxicity to normal tissue from the engineered CAR-T cells.
Statement of Benefit to California (as written by the applicant)	The citizens of California will benefit from this proposal through development of a new and potent therapy for glioblastoma (brain cancer), one of deadliest cancers known. The California economy will also benefit from this project through creation and maintenance of bio-tech jobs and the potential to export the therapy worldwide. This project will also further California's international reputation as a global leader in innovation and bio-tech.
Funds Requested	$1,414,800
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: 72

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	73
Median	72
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 proposal have the necessary significance and potential for impact?
Yes: 10	• Glioblastoma is a devastating disease with dismal outcomes. Better treatments are needed. • There is an unmet medical need for improved therapies for the treatment of glioblastoma. • The focus on glioblastoma is notable. • Branched N-glycans are overexpressed (but not tumor-specific) post-translational modifications in tumors. Reagents binding to branched N-glycans may be an effective antigen-binding tool for cancer immunotherapy.
No: 2	*none*
GWG Votes	**Is the rationale sound?**
Yes: 5	• The idea of using the proteins to target carbohydrates and a single chain variable fragment from a monoclonal antibody that pinpoints T cells does look as though this works, and enables the killing of a diversity of cancer types in vitro. • A targeted CART T cell approach could work, and there is some support through preliminary data. The limited time line of the in vivo data does not addresses tumor disappearance versus tumor onset delay. • Preliminary data demonstrates strong evidence that the targeting of breast and ovarian cancers can be effective. Little data suggesting activity in glioblastoma, sans one killing assay lacking a control treatment group. • It's unclear why the applicants propose do this in glioblastoma when the data looks so interesting in breast cancer. • Rationale for using glioblastoma as a model is not clear. • Tumor specificity is not convincing. • There seems to be an oversimplistic view of glioblastoma stem cells and how to identify them. • No mentioning of targeting cancer stem cells - they potentially use a sorting strategy that does not capture stem cells. • Attempts to target CAR-T cells to attack cells expressing high levels of branched N-glycans is interesting because of the high levels of these carbohydrate modifications on at least some cancer cells. There does not, however, appear to be any consideration of how easy it is for cells to lose these carbohydrates and remain malignant, or on the localization of these specific carbohydrates to particular cancer subpopulations. • The protein exists as a tetramer. It is unclear if the CAR exists as a tetramer and if it retains the same avidity that is important for the protein to bind. • Total flux should never be reported in linear scale. Much information is lost and it appears misleading to claim that mice are cleared of tumors when data is presented in this limited scale. • Cell counts in 10d are not equal between GlyTR1-CAR and non-transduced T cells - could also be fratricide.
No: 7	• The differential expression of the antigen tumor and normal tissue is not convincing. It is not clear why glioblastoma is being studied as there is little data for this disease. • Need to see more data to determine if the mice are tumor free. Additional data from glioblastoma would make the proposal more convincing.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 5	• The approach is reasonable to produce a CAR-T cell product. • Optimized CAR molecule, plans for changing dimerization and co-stimulation. • Use of patient-derived glioblastoma cell lines is a strength. • The paper cited as evidence that 41BB exerts tonic signaling in the absence of CD28 is misunderstood. Opposite was true, which decreases confidence. • Immunogenicity experiment explanation doesn't make much sense - no IgM but IgG is present? What was the mouse model? • Heterogeneity is not addressed.

No: 7	• The thought in this project is frequently of high quality. There is also attention paid to the importance of exploiting high avidity binding and the importance of target density. That said, there is a relatively modest level of attention to potential toxicity in the brain. • There is little attention paid to the ability of glioblastoma and other cancers to change important aspects of their antigenic phenotype while still maintaining their malignancy.
GWG Votes	**Is the proposal feasible?**
Yes: 9	• The progression to clinical trials is well understood because of the frequent use of CAR-T cells for treatment of various cancers, including gliomas. • Project is feasible and prior experience with bispecific protein supports the ability to investigate the activity of these gene engineered T cells. • The approach is reasonable to produce a CAR-T cell product. • Limited experience with glioblastomas.
No: 3	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 12	• It appears so given that "the therapeutic approach for treatment of glioblastoma proposed herein will be applicable to diverse populations. Our study design incorporates diverse populations into all of its studies." • Cancer does not distinguish between different populations, and improved cancer treatments will benefit everybody. • The research team appears diverse, and serves a diverse community, but there isn't much in the way of a described institutional commitment to DEI.
No: 0	• Not confident that there is a genuine focus on needs of underserved communities.

Application #	DISC2-13119
Title (as written by the applicant)	Development of Improved Stem Cells for Cardiac Cell-Based Therapy
Research Objective (as written by the applicant)	Development of conditioned 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. • Elucidate RNAs that are differentially expressed in age-matched male and female control stem cell-derived cardiomyocytes compared to activated cells from different ethnicities. • Successful modification of stem cell derived cardiomyocytes to produce candidate therapeutic cells. • Delivery of conditioned stem cell-derived cardiomyocytes in mice followed by longitudinal bioluminescence imaging to quantify stem cell retention. • Determine cardiac structural and electrical remodeling post transplantation. • Determine the improvement of cardiac function 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 injury can lead to lethal consequences. The current proposal will develop conditioned stem cell-derived cardiomyocyte that is resistant to cell death, leading to enhanced stem cell survival and retention for cardiac transplantation.
Funds Requested	$1,410,267
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	71
Median	70
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 proposal have the necessary significance and potential for impact?
Yes: 11	• Yes. Cardiovascular disease is a huge issue in California and most of the world. • The proposed study focuses on myocardial infarction and the subsequent risk of developing heart failure. The current treatment options are limited and novel treatment approaches are an unmet medical need. • The proposal aims to develop cells with a higher likelihood of being able to be transplanted successfully. The ability of cardiomyocytes to remain in the myocardium and functionally integrate represents a major challenge. • Stem cell-derived cardiomyocytes are being investigated as a therapy to regenerate heart function in human clinical trials. One roadblock to their success is the low level of survival of cells implanted in the infarcted heart. A technology to improve their retention addresses a critical bottleneck in advancing these therapies. • The difference in the applicant's approach from previous approaches is the targeting of the inflammasome. Hopefully, inhibition of inflammation will result in increased cell survival. If this approach works, the applicant will have addressed a critical bottleneck in the treatment of heart failure. • In response to reviews of the previous submission, the applicant has resubmitted with new data showing that activation of inflammasomes in animal models and humans leads to heart failure. • The aims are well developed and the progression from concept to a potential therapeutics are well presented. • The plan for translation involves evaluation in a more relevant [large animal] model after these exploratory mouse studies. This is logical as the [large animal] is a much more relevant model for human heart function and regeneration than the mouse. • Stem cell-derived cardiomyocytes with enhanced survivability in vivo addresses the clear unmet need of treating heart failure (e.g. myocardial infarction). • Improving survival is a clear advantage but several other key roadblocks exist, including the development of arrhythmia and functional integration.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 3	• The proposal builds on the premise that a complex inflammatory state contributes to the lack of significant beneficial effects of cardiac cell therapy with cardiomyocytes thus far. This is supported by preliminary data. • The concept of using RNAs to influence and more specifically increase the resistance of transplanted cells is sound. • The applicants provide preliminary data supporting all major concepts of this proposal. This relates in particular to the role of an inflammatory influence on cell survival. • The investigators present very strong preliminary data showing anti-inflammatory small molecules and knockout of a target enhances integration of the cells. • If successful, the proposed experiments could advance the field of cardiac cell therapy. • The premise for increasing short-term survival of stem cell derived cardiomyocytes by inhibiting the inflammasome pathway is strong. The link to long-term viability and functional restoration is less clear.
No: 9	• It is very unclear if a broad RNA approach, in which it is not clear what genes will be silenced, would be an improvement over the CRISPR approach. • A more targeted approach is needed, like CRISPR, for the cell engineering. • CRISPR should have been used instead.

	• Candidate gene approach that shows already some efficiency seems to be more promising however, this candidate approach is not further developed. • Selection of potentially relevant RNA is still not addressed, specificity is still an issue, no controls for off-target effects are described.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 2	*none*
No: 10	• Overall, the experiments are well described and justified. This relates in particular to the proposed cell experiments. The proposed rationale on how to identify relevant RNAs is well described. • Experiment design is clear and detailed. • The project makes use of in vitro and in vivo models to evaluate molecules in their ability to suppress the inflammasome and improve cardiomyocyte integration and function. • A logical path for discovery is presented. • In vivo tracking of implanted cell viability is a strength. • For the major components, limitations are discussed and alternatives are proposed. • The timeline is appropriate. • There are some concerns related to the bioinformatics analysis and the selection of which miRNAs will be selected and how a potential positive impact can be determined. • There are some concerns related to the bioinformatics analysis. This cortical component is described only very cursory. All differentially expressed RNAs will be analyzed. In the following aims, the applicants propose to use RNA overexpression. Consequently, one might expect that only over-expressed RNAs are of relevance. • For analyzing expression and the proposed targets, RNA would need to be inversely correlated. This is also not described in detail. Finally, one might have to consider the directionality of a proposed effect. If miRNA is overexpressed, target mRNA expression would need to be reduced. The reduction of target mRNAs would then need to influence the resistance to inflammation. This concept and therefore the selection of miRNAs for the subsequent aims is not well described. • The project hinges on identification of RNAs that specifically suppress the inflammasome. This may be difficult to achieve in the short timeframe of this project, and alternatives are not provided if they do not identify such an RNA. • The project could be de-risked substantially by investigating the small molecules and/or genetic knockouts used in their preliminary data. • Focus on RNA is problematic and poorly rationalized. • It is very unclear why an RNA approach has been chosen. • How can the applicant be sure that the RNA(s) being used do not have off-target effects? • In response to the previous review question of what the advantage of RNAs are over small molecules (which also work), the applicant notes the ability of RNAs to target “a network of proteins within the same cellular pathway”. This may also be a disadvantage, and it is impossible to target the response to a single pathway. • RNA should not be used for these types of experiments. • In Figure 7, it doesn't appear the hearts are really infarcted and fractional shortening is in the normal range. In Figure 9, no 'n' pressure changes without knowing HR is not helpful. • The team has to be careful to not over interpret functional restoration in the mouse model. Electromechanical coupling between murine and human cells is unlikely to provide direct functional restoration. Paracrine effects are more likely to be beneficial.
GWG Votes	**Is the proposal feasible?**
Yes: 7	• The milestones are very clearly laid out and logical toward achieving project goals. • The milestones seem appropriate, but hinge upon identification of a specific RNA. • The team is very strong, with complementary expertise in developing cardiac cell therapies from stem cells, and has a history of collaboration. • Technically feasible, but a useful targeted outcome is unlikely.
No: 5	• The milestones are logical and are likely to be achieved during the proposed timeline. • The proposal team is highly qualified to conduct the proposed experiments. All required resources are available.

	• The budget is appropriate. • It will be difficult to complete the proposed studies. For example, animals will be harvested at a 6-month time point. This will occur in year 2, which will allow the team ~8 weeks, if everything goes well, to perform the analysis.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 12	• Institutional commitment to DEI values is evident in the proposal. • Myocardial infarction and heart failure affect the diverse population of CA. Therefore the outcome is important and addresses unmet medical needs. • All groups in California are negatively impacted by heart disease, but the burden on underserved communities is especially high. Improvements in regenerating cardiac function would have significant impact. • The project will use iPSC lines from donors of different race, ethnicity, and sex, and animal models of both sexes. • The proposal utilizes various cell lines representing and including race and sex. • Six age-matched male and female stem cells of Caucasian (33-34 yrs), Latino (33-34 yrs), and African American (33-34 yrs) origins will be differentiated using the small molecule protocol to obtain stem cell-derived cardiomyocytes. I assume this means that a single male and female will be analyzed in each ethnicity, which may be too small a sample size to generate data regarding race, ethnicity, and sex. • Only three female cells lines will be examined in mice (one from each ethnicity).
No: 0	*none*

Application #	DISC2-13087
Title (as written by the applicant)	Treating acute respiratory distress syndrome by engineering phagocytic clearance of transplanted stem cells in the lungs
Research Objective (as written by the applicant)	We will develop a novel regenerative and immunomodulatory therapy using stem cells combined with biodegradable polymer particles to deliver existing anti-inflammatory/anti-fibrotic drugs to the lungs.
Impact (as written by the applicant)	The proposed therapeutic is intended to treat acute respiratory distress syndrome (ARDS) in patients critically ill from infections such as SARS-CoV-2, and also prevent chronic, long-haul diseases.
Major Proposed Activities (as written by the applicant)	• Prepare and characterize stem cell-particle-drug formulations with different drug dose and releasing profile. • Develop assays to characterize candidates for potency, purity, and identity. • Test reproducible disease modifying efficacy in an animal model that mimics ARDS hyperinflammation and fibrosis processes seen in COVID patients. • Characterize biodistribution of stem cell-particle-drug formulations and immune cell uptake in vivo. • Investigate mechanism of action (MOA) of stem cell-particle-drug formulations in restoring the immune balance to suppress hyperinflammation and prevent fibrosis processes. • Assess early safety of stem cell-particle-drug formulations.
Statement of Benefit to California (as written by the applicant)	The COVID-19 pandemic has exceeded 4.5 million confirmed cases and 66,500 deaths in California as of September 2021. Racial and ethnic minority groups including Latinos are disproportionately affected by COVID-19. Months after infection, 30% to 80% of patients are still battling debilitating lung damage and other symptoms of 'long COVID'. If successful, the proposed therapy can save 10,000s of lives and improve the quality of life of 100,000s of COVID-19 recoverees in California alone.
Funds Requested	$1,286,100
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	11
Highest	92
Lowest	50
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	1
(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 proposal have the necessary significance and potential for impact?
Yes: 9	• The proposal describes a highly innovative approach to the treatment of Acute Respiratory Distress Syndrome in COVID infection and from other causes. • The idea is to exploit endocytosis of dead MSCs by pulmonary phagocytes to provide a targeted delivery of drug to macrophages, in the damaged lung tissue. • Targeted delivery of a drug using MSCs is a novel and interesting idea. • Using MSCs as a drug delivery vehicle to increase local drug concentration is potentially interesting. • If successful, it would be an important new addition to the therapeutic armory and of significant impact.
No: 4	• The idea to exploit dead MSCs by pulmonary phagocytes for targeted delivery of drug to macrophages is interesting, however I think that this proposal should be underpinned by proof-of concept data, demonstrating that the approach is viable. • At the moment there are strong risks that such modification of MSCs will not produce the desirable results or effect will be incremental compare to MSC and drug alone or in combination. • Drug loading into MSCs may result into the modification of MSC properties and suppression of MSC production of mediators. Although authors state that MSCs viability status is not important for their mechanism of action, intrinsic ability of MSC for immunomodulation should not be completely discarded. • Authors should demonstrate that such modification results in stronger therapeutic effect compared to MSC, drug alone, or combined. Authors should prove that MSCs are indeed being engulfed by macrophages in vivo and that this process is the main mechanism of MSC therapeutic effects– at the moment this postulate remains a controversial matter in the field. • Drug has been used in clinic, not a clear novel effect.
GWG Votes	**Is the rationale sound?**
Yes: 5	• The proposal is based on the well-described observation that pulmonary fibrosis (accumulation of extracellular matrix) is the major pathogenic mechanism leading to pulmonary insufficiency and the need for ventilation in patients with COVID and other viral infections of the airways. • Existing therapeutic options rely on dexamethasone, which has a modest benefit in reducing mortality. A new approach is needed that is not dependent on viral strain, given the likelihood of new emerging strains at the moment and in the future. • Macrophages are central to the process of fibrosis in the lung. They accumulate in lung tissue as a result of virally induced inflammation and drive a cytokine storm as well as fibroblast proliferation. They are therefore the ideal target for new therapeutic approaches. • The proposal is to target pulmonary macrophages using allogeneic umbilical cord MSCs loaded with a drug formulation in which it is bound to soluble polymer particles. The concept is that MSCs will be cleared into the lung by trapping in the pulmonary micro-vascalature (first-pass effect), where they will die and in doing so will release the drug-polymer particles. • The role of the polymer will be to ensure uptake by phagocytic pulmonary macrophages. It is hypothesized (but not proven) that the drug-loaded phagocytes will be induced to anti-inflammatory, tolerogenic and regenerative pathways. • The proposed drug has some therapeutic efficacy. • There is no consensus that MSC are taken up in vivo - rationale is thus weak.
No: 8	• The project is based on an interesting idea to exploit the mechanism of efferocytosis of dead MSCs by pulmonary phagocytes after MSC administration in vivo. Authors propose to load MSCs with drug to enhance specific delivery to macrophages.

	• Preliminary data are not sufficient to support the viability of the proposed approach. Authors should demonstrate that such modification of MSCs will be beneficial compared to MSCs alone, drug alone and in combination as the drug is already a standard of care. • Not clear that death of MSCs is a mechanism of action.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 1	• The project is based on establishing umbilical cord MSCs as a delivery vehicle for drug-polymer. • The proposal is straightforward and well-planned. • Preliminary evidence are provided showing clearance of large numbers of MSCs in mouse lungs 24h after venous infusion. • Data are also provided to show drug loading into polymer particles during a 4 - 12h incubation period, dependence on size of the polymer particles, and evidence for drug release and efficacy after release. • Evidence is also provided for the feasibility of mouse models of lung inflammation and injury. • No specific evidence is provided to show that the proposed delivery of drug-polymer can modify ARDS in mouse models and the work is therefore based on a more general range of evidence. The aim of the current work is to fill that gap by demonstrating reproducible disease modifying activity.
No: 12	• Authors are proposing to develop a universal therapy for all types of ARDS, including COVID-19 induced ARDS, which is not realistic and makes the application unfocused. COVID-19 ARDS is recognized to be very different to non-COVID ARDS. • Just one bleomycin model of lung injury is not enough for clinical translation – it would rather be needed for proof-of-concept studies. • Animal models of lung disease are difficult. Additional models beyond the bleomyocin model should be used. • The animal model is not highly clinically relevant. • As dexamethasone has strong anti-inflammatory effects it is important to test in more relevant models such as live bacteria pneumonia-induced ARDS and sepsis-induced ARDS to ensure that host defense against infections will not be compromised. If authors intend to develop this as anti-COVID therapy it should be tested in Covid models e.g. K18-hACE2 mice. • In vitro studies proposed to establish potency assays using RAW cells (murine cancer cell line) are not relevant, authors should use primary human macrophages. • Risks were not assessed and specific mitigation strategy was not present. • Poor preliminary data that justify the proposed experiments. • Preliminary data is limited to expertise rather than providing supporting data for the overall hypothesis. • Translation to the clinic is not described.
GWG Votes	**Is the proposal feasible?**
Yes: 7	• The project is extremely well thought-through and designed to deliver all the data needed to progress to the translational phase. The work will be carried out over 24 months. Preliminary feedback from the FDA has been obtained and dialogue will continue at the end of the project. • The project is feasible and all techniques are available. • The proposed work can be done in the 24 months timeframe. • More relevant models should be used.
No: 6	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 12	• Mouse models will include both genders; future work in humans would take account of ethnic diversity. • No concerns.
No: 1	*none*

Application #	DISC2-13052
Title (as written by the applicant)	Autonomous System for Organoid Culture and Classification (ASOCC)
Research Objective (as written by the applicant)	We will develop an automated technology that will make it easier to make organoids by eliminating most of the human manual labor and using artificial intelligence to identify good and bad organoids.
Impact (as written by the applicant)	Our new tool will reduce variability in organoid manufacturing and identify organoids that are of high quality and can be used for scientific research or transplantation into humans.
Major Proposed Activities (as written by the applicant)	• MILESTONE 1 (Month 6): Maintain organoids in an autonomous bioreactor for 4 months. • MILESTONE 2 (Month 12): Non-invasive imaging - Acquire all images of organoids using multiple different microscopy techniques that identify different cell types and organoid health. • MILESTONE 3 (month 14): Invasive testing - Analyze the different cell types and molecules present in when organoids are 2, 3 and 4 months old. • MILESTONE 4 (Month 18): Using the non-invasive imaging information to teach artificial intelligence how to predict the quality of an organoid. • MILESTONE 5 (Month 24): Install and validate performance of the autonomous organoid bioreactor and artificial intelligence in a remote laboratory.
Statement of Benefit to California (as written by the applicant)	Common and rare diseases like macular degeneration and retinitis pigmentosa affect many Californians. The proposed tool will aid discovery of stem cell-based technologies to restore vision in people with permanent blindness and discover treatments to prevent blindness. California is a leader in science and innovation. The proposed tool will aid scientists throughout California and the world, to use organoids effectively to discover treatments for diseases affecting all parts of the human body.
Funds Requested	$679,547
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All Grants Working Group (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	5
Highest	80
Lowest	60
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 proposal have the necessary significance and potential for impact?
Yes: 7	• This novel candidate is an autonomous system for organoid culture and classification (ASOCC) that will produce reproducible and high quality organoids. There is an urgent need to improve reproducibility of retinal organoids for both research and clinical applications. • If successful the project would improve retinal organoid production for use in cell-based therapies to treat vision disorders. This is a clear unmet need since many of these disorders lack effective therapies to improve or restore vision. • Improved organoid manufacturing would address a bottleneck by reducing heterogeneity and identifying quality attribute assays to generate cells that are more likely to be effective for patients. • Translation will occur by implementing the bioreactor and imaging systems at the research institute as well as placement and evaluation at the medical center. • The project focuses on cell composition and organization. A lack of functional assessment raises concerns about relevance to cell therapies. • The proposal addresses an important bottleneck, and would enhance organ culture system approaches. • Yes. It would be helpful to identify quality organoids early in the product development process.
No: 4	• The proposal includes a plan to perform periodic microscopic imaging of live organoids, and also a plan to use computational artificial intelligence (AI) approaches to classify them. This might have some value for organoid researchers, however this plan also suffers from difficulties in how one would assign qualities (good or bad) to organoids. However, if successful, these computational approaches would have some value. • This grant might allow for improved organoid culture, with a focus on preparing retinal organoids, but at present, neither of these advances are particularly novel. • This project would not meet a currently unmet medical need. Rather, the goal is to develop an improved device for the long term culture of organoids. • This research project is unlikely to proceed to a translational stage after completion of the proposed work. • Incremental rather than transformative advance.
GWG Votes	**Is the rationale sound?**
Yes: 7	• The team has developed imaging based models to predict high resolution structure from low resolution imaging. These data support the ability to develop the models proposed. • Machine learning models have been demonstrated to relate imaging to cell organization in other applications. The premise is strong. • The rationale is sound, though not ambitious. The applicant has some experience with retinoid organoid production. • Interesting imaging based models to determine the quality of the structure from low resolution imaging. • The rationale for a perfusion bioreactor to enhance organoid maintenance in suspension is clear. • The preliminary data are somewhat limited in this application, showing some success with the production of retinal organoids. • There is a lack of preliminary data indicating that the bioreactor reduces heterogeneity or improves organoid function. • The focus on binary outcomes is problematic and does not incorporate the inherent diversity of organoids. • The study will enhance stem cell biology by improving reproducibility and production of stem cell-derived organoids.

	• The study is a logical extension of the applicant's previous CIRM funding and the extensive preliminary data presented. • In prior work the team developed a perfusion microfluidic chip for retinal organoid production. • This is an extension of existing research funded by CIRM.
No: 4	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 2	• This is a well structured study that will optimize the bioreactor for long term culture, develop a multimodal imaging platform to follow retinal organoid development and use this to develop the artificial intelligence (AI) algorithms. • The investigators have the expertise to complete the proposed study. The independent assessment of the optimized candidate at a second institute is a strength of the study. • Pitfalls and alternatives are briefly covered. However, alternatives are not considered if there are problems with heterogeneity, anti-adhesion, bioreactor modification or development of AI. • Yes, but it is not clear how the the applicant will proceed if the planned external validation is not achieved. • Yes. However, the bioreactor study results are not clear and not sufficiently promising.

No:
9
	• The project is designed to build a bioreactor and optical monitoring system to incorporate into the retinal organoid manufacturing pipeline. Overall, the planning and design are not adequate. My specific comments are
	  • The team has identified roadblocks in organoid heterogeneity and inline monitoring that must be improved.
	  • The technology would be near ready for translation. Cells produced in this pipeline would need functional validation in vitro and in vivo.
	  • Milestone 1 (bioreactor development) lacks details on design and refinement. The goal of reducing adhesion is clear but further cell characterization (including heterogeneity) is not described.
	  • The imaging plan is very detailed and well-designed to relate brightfield images to cell composition and organization using fluorescent reporters and endpoint immunofluorescence. Metabolic imaging is well-integrated.
	  • Imaging tools and fluorescent reporters are available to the project to track developmental progression in the organoids.
	  • Model structure and development (training and testing) are clearly described.
	  • The choice of binary outcomes by an expert seems arbitrary and difficult to relate to patient outcomes. Finer resolution in output data would likely have greater impact.
	  • Ideally, the quality outcomes should be related to functionality. Lack of consideration of functional phenotypes (in vitro) or performance in an animal model is a weakness.
	• If this project is successful, the result would be somewhat improved methods for organoid production. However, this does not constitute a transformative advance or position this team for translational studies.
	• The project is doable as proposed, but the advances in terms of stem cell research are fairly methodological and not terribly ambitious.
	• The research plan is not very detailed, and it is hard to know exactly what experiments and developmental goals are to be achieved.
	• This proposal contains only minor consideration of potential pitfalls and alternative avenues.
	• The heterogeneity of the organoids is not well characterized, and the basis for 'good' or 'bad' organoids needs better definition.
	• The approach should produce better quantitative output data than 'good' or 'bad' to describe the quality of the organoid.

GWG Votes	**Is the proposal feasible?**

Yes: 6	• The applicant team appears to have the necessary experience in stem cells, retinal organoids, vision loss treatment, bioengineering, and machine learning and therefore is equipped to carry out the planned experiments. • A concern is that the overall effort is spread across a lot of individuals (including two that have not been appointed) and thus the study may become fragmented. Strong oversight and management will be critical. • The applicant has been highly productive in the field of retinal organoids and has a history of successful collaboration. • Yes, though the applicant's experience is mainly with retinal organoids. The production of other types of organoids may prove difficult. • Milestones and outcomes are realistic and the investigators should meet their timelines. • Yes - the applicant has a reasonable timeline to achieve the proposed milestones. • The investigators proposed clear and quantitative milestones for all objectives. • The likelihood for achieving these milestones is high. • The proposal is not highly innovative but feasible for retinal application. • Adaptability of the approach to other organ systems remains unclear.
No: 5	• The research plan should provide more detail about integrating the different components.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 10	• The investigators acknowledge that the stem cell lines they have do not account for diversity. However, these lines make sense for use in this project. Findings should be validated in more diverse lines. • The proposal includes discussion of ophthalmological disparities, including the elevated incidence of glaucoma and retinal dysfunction in disadvantaged groups and among the aged. • The automated system can be used to generate retinal organoids from any racial, gender and/or ethnic background and will benefit underserved communities. • The project outcomes have the potential to improve treatment for vision disorders, which affect all groups in California's diverse population. • There might be some benefit to underserved groups, but such benefits would be indirect.
No: 1	*none*

Application #	DISC2-13015
Title (as written by the applicant)	Combating Ovarian Cancer Using Stem Cell-Engineered Off-The-Shelf CAR-iNKT Cells
Research Objective (as written by the applicant)	Hematopoietic Stem Cells (HSC)-engineered allogeneic mesothelin-targeting CAR-iNKT (AlloMCAR-iNKT) cells
Impact (as written by the applicant)	Treatment of ovarian cancer
Major Proposed Activities (as written by the applicant)	• Milestone 1. Production of the AlloMCAR-iNKT cells • Milestone 2. Characterization of the AlloMCAR-iNKT cells • Milestone 3. Delivery of the new therapeutic candidate
Statement of Benefit to California (as written by the applicant)	Ovarian cancer (OC) is the leading cause of death among women with gynecological malignancies. In the USA, California is the state with the highest incidences and deaths of ovarian cancer. In 2021, it is estimated that 2,550 women will be diagnosed with OC and 1,640 women will die from this disease at California. Therefore, novel therapies are urgently needed. The proposed project can potentially lead to a novel off-the-shelf cell therapy for ovarian cancer and save lives.
Funds Requested	$1,404,000
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All Grants Working Groups (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	68
Median	70
Standard Deviation	15
Highest	96
Lowest	50
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	1
(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 proposal have the necessary significance and potential for impact?
Yes: 7	• The product targets ovarian cancer (OC) which is a significant disease in incidence, morbidity, and mortality. • There is no approved immunotherapy for OC and the product would be significant. • There are several other immunotherapies for ovarian cancer in development, so this one is not the first in the space, but does address a clear unmet need. • High risk - high reward proposal.
No: 5	• The Chimeric Antigen Receptor (CAR) target is risky with an induced Natural Killer T (iNKT) cell. The iNKT cells need to be validated in patients to de-risk this off-the-shelf strategy.
GWG Votes	**Is the rationale sound?**
Yes: 6	• Use of iNKT cells is a new approach, but at this stage it is not clear if this approach will outperform the more established CAR-T approach. • It is not clear why existing CAR-T approaches are not effective. Thus, there is no strong rationale as to why the applicant's CAR-iNKT approach would be more effective.
No: 6	• The preliminary data are strong, but it is not clear that mesothelin targeting has been useful in any disease. There are no data showing that iNKT cells will be better than T cells for adoptive immunotherapy. There are no clinical data that allogeneic cells will have any advantages over autologous cells. Therefore, the rationale is based on a series of unknowns. Luckily, these questions are likely to be answered soon in a related project, and it would be prudent to wait for this clinical data. • The preliminary data showing that a mesothelin-targeted CAR-T is ineffective may mean that mesothelin is not a well-recognized T cell target, and not that CAR-T therapies are broadly ineffective in OC. • The rationale for the engineering outside of the CAR T is not clear. What is known about immunosuppressive mechanisms that impact iNKT cells? • The preliminary data are strong, but fail to address higher level conceptual issues.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 6	• Because there is another indication for CAR-iNKT cells that has progressed towards the clinic, it may be better to hold until safety, and efficacy from that project is known. • All of the steps are appropriate to produce a product. • Whether the optimal product will be produced is not clear. • This is an unproven technology.
No: 6	• Durability studies to assess sustained antitumor efficacy are needed.
GWG Votes	**Is the proposal feasible?**
Yes: 9	• Most of the studies have already been done; thus the work is feasible. • Excellent team and resources. • No concerns.
No: 3	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 9	• OC can impact minority populations. • No concerns.
No: 3	• Not clear.

Application #	DISC2-13230
Title (as written by the applicant)	Development of a Stem Cell Fitness Biosensing Nano-bioreactor to Detect Accelerated, Pre-malignant and Malignant Stem Cell Aging
Research Objective (as written by the applicant)	same as above.
Impact (as written by the applicant)	same as above.
Major Proposed Activities (as written by the applicant)	• as above • as above • as above
Statement of Benefit to California (as written by the applicant)	safety of stem cell gene therapy products
Funds Requested	$792,000
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All Grants Working Group (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	67
Median	65
Standard Deviation	3
Highest	75
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 proposal have the necessary significance and potential for impact?
Yes: 7	• The candidate is a stem cell bioreactor that enables detection of accelerated, pre-malignant and malignant stem cell aging. The main intended use of the bioreactor is to detect stem cell changes that may impact safety or efficacy of autologous lentiviral hematopoietic stem cell (HSC) gene therapy. As such, the proposal addresses an unmet need. • Yes; this bioreactor could impact gene therapy. • Overall, interesting idea.
No: 4	*none*
GWG Votes	**Is the rationale sound?**
Yes: 3	• There is a sound rationale for establishing a bioreactor to detect accelerated aging and malignancy in stem cell or progenitor populations with particular emphasis on hematopoiesis.
No: 8	• The concept of aging in this proposal is not well-considered. • The rationale fell short due to lack of preliminary data. • The relevance of stem cell age is not clear.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 0	*none*
No: 11	• Too many missing details. What is known about the CD34+ cells? What is considered young and old? How much variation is expected? • With so many bioreactors, costs and complexity may be problematic. • The investigators present a logical plan to develop and optimize the stem/progenitor cell fitness nano-bioreactor to detect accelerated, premalignant and malignant stem/progenitor cell aging. The investigators have the expertise and models to successfully complete the proposed aims. • The validity of the bioreactor was difficult to assess as it wasn't described in detail, e.g source of CD34+ cells, isolation process and their heterogeneity. What age is young v old in this model? What is the expected interindividual variation within the young and old groups and will an n=5 be sufficient? What exclusion criteria medication/other conditions will be used for CD34+ donors? • Looking at the experimental design it appears that a large number of bioreactors will be required to assess an individual CD34+ donor sample so there are concerns about how much effort is involved and whether the cost ratio is realistic. Also it is not clear if the bioreactor is a major advantage over performing the same assay in standard culture vessels. • Isolation and heterogeneity has not been discussed. • Age groups were not defined, sample size seem too low to capture variations. • Controls are not well defined. • The experimental design does not clearly indicate controls and groups. • Allogeneic versus autologous cell therapies could be better considered.
GWG Votes	**Is the proposal feasible?**
Yes: 4	• The proposed studies for Milestones 1 and 2 are achievable within the timelines. However, I am concerned that all experiments and data analysis cannot be achieved within the five month timeframe proposed. • This is a strong and productive research team with expertise in malignant reprograming, computational analyses of mutational processes, stem cells, gene therapy, and bioreactors. • No concerns.
No: 7	• Twelve independent measurements are proposed using different bioreactors - priorities are not discussed. • Good team. The Principal Investigator has large commitments to other projects.
GWG Votes	**Does the project serve the needs of underserved communities?**

Yes: 7	• The proposal considers representation of race, ethnicity, and sex in the biorepository and molecular characterization of stem cells and use of the bioreactor and the candidate would benefit the underserved communities. • Proposal strongly considers race, ethnicity, sex, and gender diversity in the biorepository and molecular characterization of stem cells used to establish the nano-bioreactor. • The applicant appears to have a strong commitment to Diversity, Equity and Inclusion values. • No concerns.
No: 4	*none*

Application #	DISC2-13026
Title (as written by the applicant)	Single-cell Assessment for Editing-associated Risk of Cancer for Clinical Use in Real-world Settings
Research Objective (as written by the applicant)	Clinical Laboratory Improvement Amendments (CLIA)-grade assay capable of obtaining a high-resolution picture of AML/MDS predisposition in any potential gene therapy subject, and tracking the subject throughout their course of treatment.
Impact (as written by the applicant)	There is a critical need for single-cell level CLIA assays that can shed light on a patient's pre-treatment risk for developing myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML), evaluate cell products, and monitor patients over time.
Major Proposed Activities (as written by the applicant)	• Installation of the single-cell assay platform. • Characterization of version 1 (V1) library preparation system. • Design and optimization of version 2 (V2) library preparation system. • Creation of gold-standard reference materials for validation experimentation. • Quality management system creation and implementation. • Final validation of assay and launch.
Statement of Benefit to California (as written by the applicant)	The diagnostic assay that we are seeking to develop through the proposed research would significantly impact the development of CRISPR-based treatments for SCD and other CIRM-funded genomic therapies targeting hematopoietic stem cells (HSC). If successful, the proposed work will lay the foundation for single-cell sequencing diagnostics to assess the suitability, efficacy, and safety of future CRISPR-based therapies, which would make transformative new gene therapies safer and more accessible to all Californians.
Funds Requested	$806,412
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All Grants Working Group (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	66
Median	65
Standard Deviation	6
Highest	78
Lowest	55
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 proposal have the necessary significance and potential for impact?
Yes: 9	• The applicants aim to develop a platform technology for predicting the long-term safety of CRISPR gene editing for individual patients. This will unlock the potential for safely targeting edited genes to endogenous stem cells, for example in the treatment of sickle cell disease through ex vivo CRISPR editing of the beta globin gene in hematopoietic stem cells. • The proposed approach would address a critical bottleneck to the use of gene editing targeted to endogenous stem cells. The applicants aim to launch their technology for point-of-care use within 12 months. • The aim is to obtain a high-resolution picture of myeloid predisposition in the individual patient, and then track that patient through the course of treatment and make data-based decisions for their care. • The platform will also identify the presence of a pre-leukemic state or the emergence of leukemia in a patient's cells, which can then be treated through early intervention. • The proposal creates technology for predicting the long-term safety of CRISPR gene editing. • Yes. Improving the safety profile of gene therapy is necessary to reduce long term secondary effects. • It is difficult to predict impact because the proposal lacks details on how the safety of new therapies will be evaluated.
No: 4	• Currently people with sickle cell disease (SCD) are at higher risk of MDS or AML, which can be an adverse secondary effect of gene therapy. No high resolution diagnostic exists for following SCD patients after gene editing-based treatment. However, the number of patients undergoing gene editing-based treatment for any disease is small at this moment. This technology would have to prove superior to other methods for CRISPR-based genotoxicity surveillance. Also, success of the project is predicated on increased adoption of SCD gene editing and ease of translation to other gene therapies.
GWG Votes	**Is the rationale sound?**
Yes: 4	• The applicant's flagship product is a single-cell sequencing system that utilizes droplet microfluidics to perform highly multiplexed PCR, cell barcoding, and targeted amplification on tens of thousands of individual cells simultaneously. When combined with next generation sequencing, as proposed, the system should detect and distinguish rare clones in AML samples. • Using a single-cell sequencing approach to search for pathogenic alleles is a good advance, but complex. The applicant will need excellent and sophisticated high throughput technology. Additional preliminary data or proof of principle is needed to make the proposal more convincing. • The logic behind the proposed approach is that single-cell sequencing to search for pathogenic alleles will better enable detection of these alleles. • The rationale is sound.
No: 9	• The need for this system, including the need for conducting single cell analyses for this purpose, is not adequately established in the proposal.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 2	• To an extent, but the applicant did not adequately identify risks and provide alternative approaches.
No: 11	• The goal and milestones are not well defined. • There are six milestones, all of which are product-development focused and straightforward. • In so far as it goes, the plan is straightforward and designed to be completed within 12 months.
GWG Votes	**Is the proposal feasible?**
Yes:	• The proposed milestones are feasible.

4	• Yes; the work is straightforward and feasible.
No: 9	• The collaboration with the applicant's industry partner needs clarification.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 11	• The writing of this proposal is attentive to CIRM's goal of serving the needs of underserved communities. • The Principal Investigator chose sickle cell anemia - which affects mostly African American populations - as the test disease for this project.
No: 2	• This is not well addressed in the proposal.

Application #	DISC2-13157
Title (as written by the applicant)	Investigate vision protection following injections of neural progenitor cells expressing GDNF at the middle stage of retinal degeneration
Research Objective (as written by the applicant)	Preserving vision by delivery of a combined neural progenitor cell and gene therapy to the majority of the retina by two subretinal injections at the time when rod degeneration has started.
Impact (as written by the applicant)	Delivery of human Neural Precursor Cell (hNPC)-GDNF by two subretinal injections at a clinically relevant time can be translated into an Investigational New Drug (IND)-enabling study and clinical trials for treating Retinitis Pigmentosa (RP), regardless of specific mutations.
Major Proposed Activities (as written by the applicant)	• In vitro characterization of hNPC-GDNF by performing neural progenitor cell markers and GDNF releasing assay, • Subretinal injections of hNPC-GDNF at dorsal-temporal and nasal parts of the eye, visual function; grafted cell distribution and characterization, photoreceptor protection will be conducted. • Dose response will be conducted by injecting hNPC-GDNF at superior-temporal and nasal parts of the eye at several doses, aiming to find the optimal dose that will be used for future IND enabling study. • Label hNPC-GDNF with cell membrane dye-PKH26 and characterize labeled cells including neural progenitor markers; check GDNF production in vitro in comparison with non-labeled hNPC-GDNF. • Subretinal injections of PKH26-labeled hNPC-GDNF or saline control into the superior-temporal and nasal parts of the eye. After functional tests, collect samples at three and six months post-injection. • Collect retinal samples for a single cell gene expression profiling and spatial transcriptomics; validate top regulated genes and proteins by labeling retinal sections.
Statement of Benefit to California (as written by the applicant)	This project delivers a combined cell and gene product at clinically relevant time for treating animal model of Retinitis Pigmentosa (RP), the most common inherent retinal disease. First, the project itself will employ new administrative, scientific personnel in California. Second, the development of this stem cell based drug ensure that the state retains its lead in the commercialization of stem cell technologies. Third, this approach has real potential to provide a treatment to Californians who suffer from RP.
Funds Requested	$1,311,144
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All Grants Working Group (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	66
Median	65
Standard Deviation	2
Highest	72

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 proposal have the necessary significance and potential for impact?
Yes: 10	• The therapeutic candidate is genetically engineering human neural progenitor cells (NPC) that, when transplanted, can slow or halt retinal degeneration. Subretinal injection of these cells offers a novel approach to retinal degeneration and could significantly improve patient care and reduce the burden of vision loss. • Three important bottlenecks will be addressed: intervention time, stem cell distribution, and halting the degenerative progression by identifying top regulated genes and proteins that play critical roles in stem cell survival and function. • Yes. However, the two subretinal injections into rat eyes that the applicant has used for proof of concept will not necessarily translate to humans, given the larger size of the human retina. • The applicant is working with a cell line product that already meets Good Manufacturing Practices. These cells have already been in humans - in patients with neurological disease - and have shown safety and tolerability. • The prior study of this product as treatment for patients with neurological disease did show an acceptable safety profile; however, there has not yet been a report of efficacy from that study. • We don't have a clinical definition of a 'middle stage' of Retinitis Pigmentosa (RP) disease. Would patients at this 'middle stage' be amenable to partaking in an efficacy trial for an invasive subretinal treatment? • Yes. Most patients who present to clinic are at Stage 2 of RP rather than Stage 1, where most therapeutic research is focused. However, the applicant does not provide a definition of 'middle disease.'
No: 2	*none*
GWG Votes	**Is the rationale sound?**
Yes: 5	• Cells have been confirmed to be safe and non-tumorigenic in both long-term preclinical studies and a clinical trial delivering the same product to the spinal cord of patients with neurological disease. This project therefore may have a low hurdle for Food and Drug Administration (FDA) approvals. The premise is solid preliminary data and published data that demonstrate the neuroprotective effect of both progenitors and Glial cell line-Derived Neurotrophic Factor (GDNF) in retinal degeneration. • The premise is solid preliminary data and published data that demonstrate the neuroprotective effect of both progenitors and Glial cell line-Derived Neurotrophic Factor (GDNF) in retinal degeneration. • Preliminary data support the idea that sustained expression of GDNF is more effective than other options. • The applicant has shown that their NPC product can survive, migrate, release GDNF, and protect degenerating neurons and photoreceptors in both rodents and large animal models. • Yes. However, the impact of prolonged GDNF release in the eye is not addressed; the product has no 'off switch' to prevent potential overexposure to GDNF.

No: 7	• It makes sense that an NPC line secreting GDNF would have a potentially beneficial effect to preserve retinal photoreceptors. However, the rationale that two subretinal injections in rat eyes would translate to two subretinal injections in human eyes does not make sense. The percent of retinal coverage with two injections in humans will be much smaller. • There is no clear clinical understanding of a 'middle stage' of RP disease. • The proposal does not mention adding immune suppression (which is not without its own potential complications).
GWG Votes	**Is the proposal well planned and designed?**
Yes: 2	• Overall, yes. However, the rationale for using two instead of one retinal injection is not quite clear, the timing of injection is unclear, and why is Stage 2 RP considered less inflammatory than Stage 1? • Milestone 1 seems redundant. • Milestone 3 is largely descriptive – it's not clear how their approach will be altered based on result from Milestone 3. • The applicant's success with previous CIRM funding is not clear; how was their previous CIRM funding used?
No: 10	• The proposal does not consider that while it is relatively easy to make sub-retinal injections to cover large areas of the rat eye, this will be far more difficult in much larger human eyes. • Milestone 3 will generate a lot of gene expression data, but it is not clear how they will be analyzed, or how the data in Milestone 3 will be used to optimize the candidate. • The potential efficacy of the therapy has not been adequately demonstrated. • No immune suppression is mentioned.
GWG Votes	**Is the proposal feasible?**
Yes: 7	• This is a productive research team with sufficient expertise in stem cell biology and animal models of retinal degeneration to complete the proposed studies. • Yes. The proposed study can be completed within the timeline proposed. • Yes. However, the progression to clinical application is not clear, and the proposal addresses neither long-term survival of injected cells nor immune acceptance of these cells.
No: 5	• A major concern: the applicant has already been awarded a large grant for an early phase clinical trial treating RP patients with subretinal NPC. Are we to assume that that trial is no longer relevant and will not demonstrate any efficacy? That trial also appears to be delayed. • The plans for translation to larger eyes need work.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 8	• The candidate is applicable for anyone with retinal degeneration, and this includes underserved communities. • Yes. This proposal addresses a large unmet need for all the reasons that the applicant outlines. • Yes. However, the candidate is a cell line, and the proposal does not include a plan to generate patient-specific NPC-GDNF. As such, race, ethnicity, and sex are not addressed. • Yes, though the applicant's response is lacking in this area.
No: 4	• No, because the applicant is only using a single cell line. • This is not specifically addressed in the proposal.

Application #	DISC2-13154
Title (as written by the applicant)	Immune evasive CAR T cells
Research Objective (as written by the applicant)	We propose a new type of cell-based treatment for glioblastoma, a very malignant form of brain tumor. The engineered cells are more selective for this tumor and provide a longer lasting response.
Impact (as written by the applicant)	This could become a new and more effective treatment for glioblastoma and is designed to facilitate access to care for larger patient populations.
Major Proposed Activities (as written by the applicant)	• Engineering of highly specific glioblastoma-targeting immune cells and testing of their tumor killing capacity. • The engineered cells are tested for longevity to provide long-lasting tumor clearance.
Statement of Benefit to California (as written by the applicant)	Treatment of glioblastoma is still largely ineffective and patients with this diagnosis have a dismal prognosis. We aim to engineer a cell product with increased efficacy and longevity to directly improve the treatment of patients in California. Also, being a major biotech hub, the area is trying to lead the world in cancer therapy, generate jobs and contribute to California's success.
Funds Requested	$1,460,270
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	65
Median	65
Standard Deviation	1
Highest	65
Lowest	60
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 proposal have the necessary significance and potential for impact?
Yes: 5	• Glioblastoma is deadly. • Advance is to start from blood cells rather than iPS cells, which will improve safety. • Generation of a "universal cell."
No: 6	• Innovation in this proposal is the expression of a truncated molecule. Other antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) eliminating/preventing technology have recently been published with higher potential for impact. • Other elements of proposal are previously published and utilized by many groups.
GWG Votes	**Is the rationale sound?**
Yes: 3	• This a lot of edits to the cells and intermediate analysis might be helpful.
No: 8	• Problem statement starts with an assumption that most CAR studies in solid tumors has used allogeneic cells that are rejected by the immune system. • Preliminary data shows that truncated molecule expressing CAR T cells are not eliminated by ADCC. Unclear how T cells impedance was measured since these systems are optimized for adherent and not suspension cells. • It is not clear what the rationale is for many of the proposed engineering tasks.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 1	• Relationship between the collaborative groups is unclear. • Applicant uses an inappropriate tumor model that is unlikely to turn on CAR T cells. • Poorly written.
No: 10	• The positive cell line to be used in this study will be generated by transduction of wild type receptor and then targeting with EGFRviii-SynNotch T cells. EGFRviii-specific T cells do not recognize WT EGFR. The other PI listed must not have read this proposal - would have identified this fatal flaw. • Only expects 10% of the starting cell product, will lose 90%. No planned experiments to determine percent of those 10% of cells that have translocations due to the three double strand breaks. • Small error but NSG mice are from Jax and NCG mice are from Charles River, whose webpage uses identical language of “lack of functional/mature T, B, and NK cells, and have reduced macrophage and dendritic cell function”. • No discussion given to ability of NK cells to kill based on missing self. • Task 3 is poorly described. No information of how the immune response will be measured. • There is no strategy for the examination of all of the proposed changes. • The animal model is of unclear relevance. • The examination for off-target genetic changes is limited. • The tumor target is not correct.
GWG Votes	**Is the proposal feasible?**
Yes: 4	• The proposal is feasible, but of unclear significance.
No: 7	• Lead PI has no experience with CAR T cells. • Given the wrong target antigen, not feasible at all.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 10	• The entity commitment to DEI values is evident, however the proposal does not describe how underserved communities will be involved in the research.
No: 1	• No genuine thought given to how this technology could address the needs of underserved communities.

Application #	DISC2-13000
Title (as written by the applicant)	Quantitative and High Throughput Hematopoietic Stem Cell Purification
Research Objective (as written by the applicant)	This proposal is for a manufacturing tool to more rapidly and efficiently purify stem cells from blood.
Impact (as written by the applicant)	Implementation of this tool can reduce production cost and enable more customized and precise stem cell therapies to be made.
Major Proposed Activities (as written by the applicant)	• Demonstrate the capability of our ratcheting system to isolate rare stem cells • Demonstrate scalability to large blood quantities • Show superior performance compared to competing technologies • Demonstrate capability to sort multiple cell types at once • Demonstrate large scale sorting of multiple cell types at once
Statement of Benefit to California (as written by the applicant)	Development of this technology will work synergistically with other cell therapy production efforts to reduce the cost of cell therapies and make them more accessible to underserved socioeconomic groups in California. Furthermore, as a small business in California, we can greatly benefit the state with this proposed technology by providing jobs and expanding the capabilities of cell therapy production facilities in the state.
Funds Requested	$499,680
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All Grants Working Group (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	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 proposal have the necessary significance and potential for impact?
Yes: 4	• Overall, the panel seeks evidence that the proposed device will outperform existing devices on the market at existing tasks. • Why is there a need for purified stem cells? Don't most current applications work well even if the stem cells are not pure? • This tool offers competition to current systems and offers some advantages over current systems. • Not clear if multiplexing would be an advantage if feasible.
No: 7	• The applicants suggest that many thousands of HSPC transplants performed each year could benefit from HSC purification. I don't believe this is true, since most HSPC transplants are autologous and purification of HSC for graft-versus-host disease (GVHD) prevention is unnecessary. Hematopoietic Progenitor Cell (HPC) graft engineering takes a small niche in clinical stem cell transplantation since many centers now perform a post-transplant cyclophosphamide course instead of HPC graft engineering. • The proposed technological platform would not address an unmet medical need because the need has been addressed by currently available devices that are approved by the Food and Drug Administration (FDA). But, the proposal may address a technological need - to break the monopoly on these devices. • The competitor device on the market has similar throughput, good yield, and high purity already (reference: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3762249/). The applicant's claims about lower cost do not have supportive evidence. The only obvious advantage over the competitor is the ability to conduct multiplex sorting in a single run. • Taking into consideration the massive development in T-cell-based therapies, the proposed technology would be more impactful in immunocellular therapy of cancer. • The impact of the project on the clinical Hematopoietic Stem and Progenitor Cell (HSPC) field is overstated. • The claims for added value relative to state-of-the-art do not seem accurate.
GWG Votes	**Is the rationale sound?**
Yes: 4	• The rationale of using a new technological platform (ratcheting digital cytometry, magnetic sort-on-chip) for the purification of small cell populations is sound. • The applicant should consider citing one or more review articles on stem cell purification technologies. How does magnetic ratcheting compare to: fluorescence activated cell sorting (FACS), magnet-activated cell sorting (MACS), pre-plating, conditioned expansion media, density gradient centrifugation, field flow fractionation (FFF), dielectrophoresis (DEP), improved aqueous two-phase systems, systematic evolution of ligands by exponential enrichment (SELEX), and other microfluidic platforms? • In response to reviewer comments on the primary submission, the applicants added Figure 6 to demonstrate a comparison of their kit versus a commercially available kit for purification of CD34+ stem cells. There are a few issues that make this Figure difficult to interpret: (i) dot plots are not labeled, (ii) the starting material does not look the same, though it should be the same parent source, and (iii) the competitor's kit performed poorly compared to its manufacturer's description, suggesting these measured rates may lack reproducibility. • Although current actual costs may be difficult to describe, the applicant should provide enough detail and extrapolations of future cost to support their claim that this system will ultimately be cheaper. The applicant should also clarify why costs cannot be described currently. Are they a trade secret? Are they difficult to compute? Some other issue? • More quantitative information on purification results would be useful, particularly as compared to existing technologies.
No: 7	• The applicant does not demonstrate multiplexing in the proposal, though multiplexing is claimed as an advantage of their system. • It's not clear from this proposal as written.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 1	*none*

No: 10	• The applicants propose a new sorting technology for the purification of HSPC in the clinic. Therefore, the experiments should be designed to perform a direct head-to-head comparison of the applicant's technology with the one current clinical standard. The applicant does not need to make comparisons to additional kits for CD34 purification, which they propose to do in Milestone 3. • The critical experiment (to prove the major advantage of this technology over the current standard) is multiplex sorting. But the choice of the experiment (CD34 positive selection with simultaneous T-cell depletion) is not ideal, because the selection of CD34 alone with purity > 90% would deplete most of the T-cells. It would be better for proof of principle to use two or three markers for positive selection (for example CD45RA / CD34) or two markers for negative selection (for example CD19 / CD3 cells). • The applicant needs to demonstrate cell viability in their system. • The proposal includes some misquotes and poorly rendered preliminary results. • The preliminary data is not strong enough to motivate the proposed work.
GWG Votes	**Is the proposal feasible?**
Yes: 4	• All experiments planned in the proposal look feasible to perform within two years.
No: 7	• More data with their own instrument would inspire higher enthusiasm on the feasibility of the proposed work. • It's not clear from this proposal as written.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 8	• Yes. However, since everyone must follow federal and state discrimination laws, stating that they follow these laws does not address the intention of this question. • The applicant states that they will work to ensure the system performs consistently across a spectrum of donors with varying age, sex, and ethnicity.
No: 3	*none*

Application #	DISC2-13194
Title (as written by the applicant)	Generating a transplantable synthetic kidney from human induced pluripotent stem cells
Research Objective (as written by the applicant)	A revolutionary solution to the shortage of kidneys for transplantation: A synthetic kidney, that is scale-up engineered from human iPSC-derived self-organizing kidney progenitor cells.
Impact (as written by the applicant)	This novel therapy could profoundly impact the health and lives of the one in seven Americans with chronic kidney disease, as well as the two in one thousand Americans with end-stage renal disease (kidney failure).
Major Proposed Activities (as written by the applicant)	• To optimize the synthetic kidney self-organization system • To characterize the self-organizing synthetic kidney in vitro and in vivo • To scale-up engineer a basic synthetic kidney with a 3D-printed tubule-like scaffold • To characterize the basic scaled-up synthetic kidney in vitro and in vivo • To scale-up engineer an advanced synthetic kidney with a 3D-printed tree-like scaffold • To evaluate the safety and efficacy of the advanced scaled-up synthetic kidney in a preclinical small animal model of chronic kidney disease and end-stage renal disease
Statement of Benefit to California (as written by the applicant)	As a novel kidney replacement therapy, the synthetic kidney approach will be able to provide off-the-shelf stem cell-derived transplantable kidneys for California citizens with end-stage renal disease (ESRD; i.e. kidney failure; prevalence is 2 in 1000). The synthetic kidney will also be able to slow or halt the progression from chronic kidney disease (CKD) to ESRD for California citizens with CKD (prevalence 1 in 7). This new therapy will have dramatic health and life impact on these patients and will save billions of dollars of healthcare cost for patients with CKD and ESRD in the United States.
Funds Requested	$1,401,638
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All Grants Working Group (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 proposal have the necessary significance and potential for impact?
Yes: 8	• This proposal will create a synthetic kidney from a 3D matrix and stem cells differentiated into kidney cells. The aim is to replace dialysis and reduce or eliminate the need for donor kidneys. This is a bold proposal and much can be learned from pursuing this line of research. • The path to translation carefully considers optimization of nephron structure and organization, subunit assembly via 3D printing, and evaluation in vitro and in vivo. • Other competing methods to address this issue including xenotransplantation of kidneys from animals to humans is progressing rapidly, making this proposal a long shot. • If successful the project has the potential to revolutionize treatment of kidney diseases, which is currently limited by the number of donor organs available. • The work here would increase the likelihood of developing synthetic kidneys for stem cell-based therapies to treat kidney disease. However, it is unlikely to lead to a translational project in the near term.
No: 7	• The proposed technology is to develop a synthetic kidney prototype as proof of concept for therapy. The basis for the technology comprises human pluripotent stem cell derivatives that express features of kidney progenitor cells. The project is at an early stage and lacks adequate preliminary data to support most of the proposed aims, including the demonstration of therapeutic efficacy. Due to the challenging nature of this work it is hard to see how this project could lead to a proof of concept at this stage. • This project is too early stage for this award; the approach needs more development.
GWG Votes	**Is the rationale sound?**
Yes: 5	• No concerns.
No: 10	• The use of the remarkable endogenous development and self-assembly ability of iPSC-derived kidney progenitors and organoids is compelling for engineering kidney tissues and organs for transplantation. • The premise that these stem cells can spontaneously form transplantable embryonic organs in vitro that would fully mature in vivo remains highly speculative. • Human pluripotent stem cells may provide a way forward for kidney disease, if they can be coaxed into forming functional structures. The hope here is that with bioengineering the stem cells may do so. • It is not exactly clear why the bioengineering is necessary, or what the real advantage of the synthetic kidney would be over a transplant. • Preliminary data suggest that the synthetic kidney organoids contain major kidney cell types and generate organized structures. • Preliminary data do not yet establish the feasibility of assembling synthetic kidney structures into higher order tissues or organs, or effectiveness in vivo that would reassure me that the applicant can meet their goals. • The applicant's preliminary data show their ability to produce cells that self-assemble into an organoid. These organoids appear to have some functions replicating native kidney function. Their plan is to increase the size of the organoid. This has not been tested, but appears to be possible; the applicant offers several strategies. • The preliminary data are not adequate for most aspects of the proposal. • Recent advances in ureteric progenitors from iPSC opens the possibility of engineering a urine drainage system within engineered kidneys. • Complexities of draining the urine to the bladder will be challenging, but potentially surmountable.
GWG Votes	**Is the proposal well planned and designed?**

Yes: 4	• The progression from one milestone to the next is logical and covers the necessary ground. • Each milestone is dependent on the previous milestone; setbacks in the early milestones will make it difficult finish the work on time. • No concerns.
No: 10	• The project is well-organized from optimization of synthetic kidney subunits to assembly of subunits into organs to evaluation in vitro and in vivo. • Cell and organ assessment at the molecular, structural, and function level is detailed. • The complementary use of in vitro and in vivo analyses is a strength of the approach. • At a high level, the use of developmental principles and engineering approaches (here, 3D printing) is a good direction for the field of organogenesis. • Pitfalls are anticipated to some degree, but the proposal is relatively vague on these. The investigators may be underestimating the challenges involved in growing a synthetic kidney. • The major weakness of the project design is the unrealistic timeline of the challenges of going from progenitor cell differentiation to full organ development and testing. • No details are provided about what parameters will be optimized to increase nephron production in Milestone 1. It is concerning that the factors that effect nephrogenesis are not yet known, which raises doubts about the proposed timeframe. • Vascularization is a concern. While vascular structures have been shown to develop at the organoid level, higher level vascular network formation is not sufficiently considered in this project. • Ductal morphogenesis is hypothesized to occur spontaneously. It isn't clear how the project will proceed if this does not occur. • The investigators acknowledge the challenges of transitioning from in vitro to in vivo but their planned tactic of adding culture medium components during this transition is unlikely to be effective. • Limited preliminary data; translation to clinic questionable. • This project is too early stage for this award.
GWG Votes	**Is the proposal feasible?**
Yes: 1	*none*
No: 14	• The applicant team is outstanding: It comprises leaders in nephron development, kidney disease and transplantation, stem cell biology, and 3D printing. • This is a strong applicant team with complementary expertise that covers the range of knowledge needed to create successful outcomes. Some technicians and post-doctoral fellows appear yet to be appointed, which will further stress timelines. • My major concern is the amount of development work required to make a functional kidney, especially for a human. • The milestones and outcomes are well considered, but this is a very complex project not likely to be achieved within the proposed timeline. • The milestones are clearly detailed and logical. • Completion of the proposed milestones in a two year timeframe is unrealistic, especially given the contingent nature of study design. • There are many pitfalls in this proposal that could create barriers to success – from creating enough nephrons to the stiffness and length of the conduit. What if the conduit kinks? Or if only some of the nephrons drain into the conduit? Could ectopic urine drainage create toxicities? • Animal experiments are complex (as they require two surgeries). A lip or ridge on the end of the conduit (ureter substitute) may provide an easier anchor for suturing. As planned, this is not an easy surgery. • There is a lot of work scheduled and the budget will be tight. If there are setbacks, there will not be enough money to complete all experiments. • Success is hard to predict given the safety issues associated with human pluripotent stem cells. By the time this project reaches fruition, other types of cells with superior therapeutic qualities might be available. • It's not clear at this point if this project is feasible in the near future.

	• The project is too complex to be completed in two years. • The chance of success is very slim.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 12	• Kidney disease affects underserved communities disproportionately. Improved cell-based therapies would serve unmet needs of these communities. • The project notes that prevalence of kidney disease is higher within certain demographic populations. However, whether or not an expensive regenerative therapy could reach such populations is not considered. • The project will use animals of both sexes. The investigators acknowledge the need to consider diversity in stem cell lines in future work. • No concerns.
No: 2	• Kidney disease affects racial and ethnic communities to a greater extent and this would create a larger benefit to the underserved. • Cells from various ethnic groups are not used in this project plan, but it may be too early to do so in this proposal.

Application #	DISC2-13199
Title (as written by the applicant)	Development of a direct induction-based test for lithium response in mood disorders
Research Objective (as written by the applicant)	We will develop a stem cell based test to predict whether a patient with a mood disorder (major depression and bipolar disorder) will respond to treatment with lithium.
Impact (as written by the applicant)	Presently, many patients with mood disorders suffer through a series of medication trials over several years. This test will shorten that time patients by predicting their response to lithium.
Major Proposed Activities (as written by the applicant)	• Successful transformation of blood cells directly to brain cells • Detection of neuronal electrical activity and other measures of neuron function • Demonstrate that lithium normalizes abnormal neuron firing but only in cells from patients who responded to lithium • Optimize the assay for future larger scale research and clinical trials
Statement of Benefit to California (as written by the applicant)	This work will improve treatment and reduce suffering of the approximately two millions Californians who suffer from mood disorders. It will also lead to a company that will generate jobs and enhance the biotech environment of California.
Funds Requested	$649,975
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All Grants Working Group (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	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 proposal have the necessary significance and potential for impact?
Yes: 5	• This diagnostic would be very powerful and reduce costs and suffering. • The proposal addresses a large unmet need; predicting patient outcomes to lithium (Li) would be a major advantage in stratification of patients. • Yes, treatment of mood disorders is largely based on a "hit and miss" approach; sparing non-responders the side effects of Li is an important goal.
No: 7	• It does seem that the assay the applicant is developing is needed. The idea of a cell-based screening tool is sound and simple; the success of the applicant's transformation technique is the rub. • If successful, this methodology has potential for enhancing drug selection and, potentially, diagnosis of various disorders. However, the applicants have not yet begun any aspect of this project, which will require substantial development and optimization. • It's not clear whether this tool will change clinical practice – would clinicians use this diagnostic in place of a trial prescription?
GWG Votes	**Is the rationale sound?**
Yes: 1	• The rationale is sound, but very high risk.
No: 11	• The rationale is flawed. The applicant showed previously that hyperactivity of neurons that were derived from clinically Li-responsive patients could be selectively diminished by Li treatment in vitro. However, this result does not establish predictability as the patients had been exposed to Li already and were thus not I. The applicant now wants to discover which I patients will respond to Li using previously untreated neurons derived in vitro. • There are flaws in this proposal which range from the concept itself (the platform may not offer a significant advantage in terms of time for testing patient responsiveness) to the development of the technology (transduction of blood cells into neurons). • The proposed project will not produce a new therapy, but a screening platform to determine if patients will respond to lithium as a treatment for mood disorders. This is currently completely conceptual but, in time, is likely to assist with the selection of optimal therapies for patients with bipolar disorder and major depression disorder. • There are no preliminary data to support the feasibility of the project. • The applicant does not provide preliminary data indicating that their transformation method will work.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 0	*none*
No: 12	• The applicant does not provide any preliminary data. The applicant's team does not currently perform the direct induction protocol routinely in the lab, but they mention that their collaborator is an expert in direct neuronal induction and will assist the team in setting up the transformation protocol. However, their collaborator has induced neurons from fibroblasts, not from blood cells. This adds another layer of complexity to the project. • I am concerned about the ability of the team to perform the proposed experiments. Additionally, all studies are contingent on the success of the proposed direct induction method, and failure to meet this milestone will jeopardize the entire project. • If the proposed transformation methods should fail, the applicant will need to move forward using current methods of transformation that use fibroblasts. According to the proposal, this will not work at high frequency (~6%). • The applicant has little in the way of alternative approaches should the transformation method from blood not work. • The team anticipates that direct induction will yield a cell population that is approximately 6% neurons, as reported in other studies using fibroblasts or blood cells as source material. This raises the question of whether the proposed screening platform will be truly representative of human neurons, i.e., what are the other 94% of the cells and how will they influence the diagnostic's response to lithium? • The focus on directly transforming lymphocytes into cortical glutamatergic neurons in patients with mood disorders is interesting, but it is not clear what clinical advantage this would provide.

	• The project is entirely based on published literature and is not substantiated with preliminary data. • There are no preliminary data.
GWG Votes	**Is the proposal feasible?**
Yes: 0	*none*
No: 12	• It is not clear when the team will conclude that neurons cannot be successfully generated from lymphocytes. I worry that the team will continue to pursue a technique that will not work. I do see that Quarter 2 in Year 1 is when success of the transformation method will be determined. • Pitfalls are not adequately addressed. The alternative approaches that the applicant does suggest are not compelling: If neurons do not show hyperexcitability, what is the point of inducing excitability via artificial hyperpolarization? This goes against the rationale of using patient cells that recapitulate disease in a dish. • It's difficult to tell as written. Additional information about next steps would be useful. • It is not clear whether the transformation will work; there are no preliminary data.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 10	• The proposed technology would serve all patients, assuming that the cost is not prohibitive. However, the pilot work does not take the needs of underserved communities into account. Validation experiments will need to be performed on samples collected from patients with different ethnic backgrounds and underserved groups before the proposed tool can be used. • The initial planned studies will include male and female participants. The applicant mentions having access to a large bank of patient lymphocytes collected from donors with different ethnic backgrounds, in particular Hispanic populations. The applicant plans to validate their technology using these multi-ethnic samples. • The applicant notes that the team has access to populations with varying age, sex, racial, ethnic, socioeconomic, and cultural backgrounds. The application discusses future validation in a Hispanic population. However, only the initial validation (in non-Hispanic women) is included in the current milestones. • Yes. However, conducting a validation study of identical design using only participants who self-identify as Hispanics could be unintentionally problematic – members of the Hispanic cohort may see this positively or negatively. • According to the proposal, Hispanic samples will only be examined if time allows.
No: 2	*none*

Application #	DISC2-13100
Title (as written by the applicant)	Using diverse patient-specific hiPSC-derived lung organoids to identify the earliest lung cancer-initiating cells and events as potential drug targets
Research Objective (as written by the applicant)	A diverse patient-specific mini-lung system that identifies the earliest cancer-initiating cells and molecular events (within a tumor niche that emulates the patient's) as potential therapeutic targets.
Impact (as written by the applicant)	The present lack of reliable and predictive preclinical models for cancer, prompting the National Cancer Institute to look to stem cell biology for "Next Generation Cancer Models"
Major Proposed Activities (as written by the applicant)	• Prove that lung cancer can emerge following genetic perturbations into stem cell-derived patient-specific mini-lungs that emulate normal lungs invested with inflammatory cells and blood vessels • Screen the tumor-bearing lung organoids against known effective anti-neoplastic drugs • Turn a lung cancer cell back to a normal pre-cancer cell that might have existed in the embryo and allow cancer to re-emerge under scrutiny in a mini-lung made from those stem cells • Characterize the molecular fingerprint of each of the above mini-lungs before and after cancer emergence, and before and after drug treatment • Clinical correlation of our experimental data with the actual drug responsiveness and outcomes of patients whose primary lung cancers were obtained from a cancer biorepository
Statement of Benefit to California (as written by the applicant)	The lack of reliable preclinical cancer models has not only hampered our understanding of the roots, and hence potential therapeutic targets, of lung cancer, but has also permitted failed drug treatments. Lung cancer affects certain racial, ethnic, and socio-economic groups disproportionately, groups that unfortunately make up much of the California population. The burden in lives destroyed and resources squandered must be reversed.
Funds Requested	$660,246
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All Grants Working Group (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 proposal have the necessary significance and potential for impact?
Yes: 4	• Lung cancer is a major problem.
No: 9	• It's not likely that this proposal will be successful. There are many well-documented technical difficulties in reprogramming cancer cells into pluripotent cells. • It's not likely that this will be a feasible and effective drug screening method for patient treatment plans. • The significance of the work is poorly presented in the proposal.
GWG Votes	**Is the rationale sound?**
Yes: 0	*none*
No: 13	• Lung organoids can be generated from induced Pluripotent Stem Cells (iPSC). • Lung organoids can be genetically engineered with oncogenic mutations. • Significant effort and technologies will be required to identify each oncogenic mutation in patient tumors, integrate those specific mutations in induced Pluripotent Stem Cells (iPSC) generated from the same patients, and identify tumor initiating cells. • The five month timeline for patient treatment is not feasible. • Neither technique proposed will produce a relevant model suitable for drug screening. • In preliminary studies, the applicant shows that the original tumor was not recapitulated when gene expression or epigenetics were investigated. Thus, it's hard to understand how the approach will be relevant for drug development. • Challenges that have been identified in reprogramming of cancer cells are not at all considered in the proposal. • The rationale is poorly presented.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 0	*none*
No: 13	• Milestone 3 is not well developed. Based on this I have low confidence that the applicant has adequate access to patient samples and treatment records. • The description of CRISPR-KI in the proposal demonstrates poor understanding of this gene editing technology. • The proposal lacks details, clarity on the gene editing approach, and clear figures. Some figures are not legible. • The scientific basis of the proposal is flawed. • The applicant's grantsmanship needs work. • The preliminary data are not well presented.
GWG Votes	**Is the proposal feasible?**
Yes: 1	*none*
No: 12	• There is no evidence that cancer cells can be reprogrammed to pluripotency and then differentiated back to the same tumors. • This is a highly ambitious proposal requiring many technologies. I have low confidence that all of these can be performed monthly on patient samples, or that data analysis will be performed quickly and well. • The model development is poorly planned. • The proposal is overly ambitious for a two-year period, and has some unfocused endpoints.

	• Too many assays are proposed for the two-year timeline. • This is a lot of work for the timeline.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 10	• The applicant team appears to embrace Diversity, Equity, and Inclusion values. • The proposal makes a case for potential benefit to underserved groups, though it is unclear how diverse communities are reflected in the project plan.
No: 3	• The applicant proposes to use diverse tumor samples in Milestone 2. • The applicant states that they are committed to using diverse patient samples and addressing underserved communities, but that using diverse patient samples within this proposal would reduce study rigor.

Application #	DISC2-13125
Title (as written by the applicant)	The Pluripotent hESC-based Innovative Platform Enabling Regenerative Medicine Advanced Therapy for Amyotrophic Lateral Sclerosis
Research Objective (as written by the applicant)	The research objective is to establish preclinical safety and efficacy of our hESC-derived product for nerve tissue and function restoration as a regenerative medicine advanced therapy for ALS.
Impact (as written by the applicant)	This project enables clinical translation of hESC technology and intellectual property as a much-needed solution for ALS, having a groundbreaking impact on advancing medicine, improving human health.
Major Proposed Activities (as written by the applicant)	• To demonstrate the product is a homogeneous population of neuronal progenitor cells. Milestones: >90% positive for 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 product yields neurons with high efficiency and further progresses to motor neurons (MN). Milestones: >90% of the NRMAT product differentiates into neurons, with >50% into MN. • To establish in vivo safety of the product in an animal model of ALS. Milestones: A lack of tumors and inappropriate cell type formation (<1%) will be assured to demonstrate safety. • To establish in vivo efficacy of the product for MN regeneration in an ALS model. Milestones: >50% survives and differentiates into MN to mediate nerve repair, restore function, extend life. • To generate the target product profile (TPP) for the product. 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)	ALS is a devastating, fatal, and most costly neuromuscular disease with no cure and no effective treatment. This project enables clinical translation of hESC technology/IP as a much-needed solution for ALS. The outcome will impact the translational research priority of the CIRM by presenting the hESC therapy product as a novel, advanced strategy for a wide range of incurable or hitherto untreatable neurological diseases, thus bringing tremendous benefits to California economy and healthcare.
Funds Requested	$899,200
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	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 proposal have the necessary significance and potential for impact?
Yes: 3	• Amyotrophic Lateral Sclerosis (ALS) currently has no effective treatments and this would represent a major advance, but it is not clear at this stage if these cells can produce functional motor neurons. • Methods and information obtained from this proposal is likely to be valuable to other similar diseases and indications.
No: 9	• The strength of the proposal is the technology to generate a relatively pure population of motor neurons. These will be very useful for ALS and other research. • The major concern is that there seems to be little or no recognition of the problems surrounding the idea of replacement of motor neurons for ALS. These neurons will not only be placed in a potentially hostile environment, but they would have to survive and extend axons to appropriate muscle groups, which is unlikely or impossible. Thus, this is not a treatment for ALS.
GWG Votes	**Is the rationale sound?**
Yes: 0	*none*
No: 12	• The neuronal progenitor cells are interesting and preliminary data for the production appears strong, but it is not clear to me if ALS is the correct disease indication. • The rationale for motor neuron replacement for ALS is fatally flawed. • Do implanted motor neurons really grow to re-attach to the muscle cell? Are there other potential mechanisms of action? Without support cells, how will the motor neurons survive over the longer term? • No. There is no basis for the rationale provided. I think there is a consensus that for ALS, cell replacement would be more desirable than simply improving the environment. However, the preliminary data provided is not convincing that this platform is unique and game changer, as stated by the PI. • The large majority of preliminary results are in vitro. There is only one figure showing engraftment in the SOD mice, and this is very small. Thus, although the project may be of interest, the preliminary data are not compelling. Although the PI stresses throughout the application that this technology is much superior to current cell-based strategies being tested, there is no clear evidence in the proposal that this may be the case.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 0	*none*
No: 12	• Though the design for the generation of motor neurons seems fine, the progress toward a therapeutic intervention is not well thought out. There is no recognition of the problems with the SOD1 rat (variable onset, unstable mutant SOD1 expression, rapid onset to death). • Efficacy tests are conducted in pre-symptomatic rats, this may cloud effectiveness of the product. The animal model has lots of variability, which will make data interpretation difficult. • In the animal studies, a control should include a different cell type.

	• No indication that there is a concern for toxicity of astrocytes, microglia, oligos, endothelial cells as a barrier to MN survival. • The applicant only proposes RNA-Seq of ESC-derivatives and transplantation in pre-symptomatic ALS rats. There are only 2 aims, one focuses on RNA-Seq of in vitro generated cells and the other on the transplantation of these cells in SOD rats prior to the development of symptoms. Therefore, the experimental plan is pretty narrow. The PI mentions that by the end of this 2 year project, they will be ready for an IND-submission but this is not realistic based on the preliminary data and the experimental plan proposed here. • They aim to have 50% of cells survive and differentiate into motor neurons; this would appear to be a very high bar to achieve. Their suggested alternative approaches are excellent, but would add significant time and costs to test. • Potential pitfalls are presented but alternative approaches are not well developed.
GWG Votes	**Is the proposal feasible?**
Yes: 1	• The proposal is feasible, but will not result in a tenable therapeutic product. • The proposal is feasible but the premise is flawed, and results will not be meaningful for the development of a therapy for ALS.
No: 11	• The in-life study is appropriately long. The work is done at a CRO, which assumes they understand the model and primary outcome measurements. As long as scheduling with the CRO is not an issue, the work can be done in the timeline proposed.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 9	• The project plan has a well developed plan to account for race, ethnicity, sex and gender diversity.
No: 3	• Not really. If it does not lead to a therapeutic, then it does not serve the needs of any ALS patient. • There was no discussion of this aspect in the application.