APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Resubmission	Previous CIRM Funding	Area of Impact
DISC2-14935	Orthogonal IL2 Receptor Transduced Regulatory T Cells for Clinical Application	**$1,920,652**	**Y**	**93**	93	5	85	100	14	0	N	N	Development of a gene-edited cell therapy to improve tolerability of transplanted stem cells or organs
DISC2-15120	Gene-corrected human microglia for the treatment of adult onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP)	**$1,417,948**	**Y**	**90**	89	4	85	97	15	0	N	Y	Development of a gene-edited, iPSC-derived microglial cell therapy to treat a rare brain disease
DISC2-15119	Drug discovery for gastrointestinal motility disorders using hPSC-derived enteric ganglioids	**$1,954,367**	**Y**	**86**	86	2	80	88	14	1	N	N	Development of iPSC-derived models of the intestine to screen for small molecule drug candidates
DISC2-14982	Treatment of Myasthenic Syndrome due to Choline Acetyltransferase Deficiency Using AAV9-mediated Gene Therapy	**$1,500,000**	**Y**	**86**	84	5	75	90	9	6	Y	N	Development of a gene therapy to treat muscle weakness caused by a defect in the choline acetyltransferase gene
DISC2-15010	C9orf72 repeat expansion-tuned allelic suppression by CRISPRi as an ALS therapy	**$2,274,768**	**Y**	**85**	85	5	70	92	13	2	N	N	Development of a gene therapy to treat ALS caused by repeat expansions in the C9orf72 gene
DISC2-14897	Assessing the Functional, Immunologic and Microbiologic Characteristics of Human Livers Created in Chimeric Pigs	**$2,736,590**	**Y**	**85**	85	5	77	92	11	4	N	N	Characterization of livers derived from human stem cells and grown in chimeric pigs that could be used for transplantation
DISC2-15137	Inhibitory interneurons derived from human induced pluripotent stem cells to treat stroke	**$2,140,122**	**Y**	**85**	84	4	75	90	10	5	N	Y	Development of a product consisting of iPSC-derived interneurons within a hydrogel to restore function after stroke
DISC2-14907	A First-in-Class Treatment for Progressive Multifocal Leukoencephalopathy Via Multimodal Immune System Engineering	**$2,182,396**	**Y**	**85**	84	5	78	93	7	7	N	N	Development of a gene-edited cell therapy targeting a virus that causes a rare and severe brain infection
DISC2-14899	RNA-based therapeutics to augment regulatory T cells: a novel approach to treat myocarditis	**$2,264,509**	**Y**	**85**	83	2	80	85	8	7	N	Y	Development and selection of a nucleic acid therapy that acts on immune cells to treat inflammation in the heart
DISC2-14963	Development of an Optogenetic Vision Restoration Gene Therapy Using an Engineered Form of Melanopsin	**$1,150,820**	**Y**	**85**	83	5	75	87	8	7	N	N	Development of a gene therapy to treat blindness caused by photoreceptor loss
DISC2-14900	Developing a breast cancer stem cell drug	**$2,293,051**	**N**	**84**	83	4	78	90	6*	8	N	N	
DISC2-15114	Development of a VAV2 antisense oligonucleotide (ASO) treatment for ALS	**$2,296,376**	**N**	**84**	81	8	70	90	7*	8	N	N	

APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Resubmission	Previous CIRM Funding	Area of Impact
DISC2-14910	Human induced pluripotent stem cells-derived glial enriched progenitors for the treatment of mild traumatic brain injury	**$1,931,806**	**N**	**83**	83	1	80	85	1	13	N	N	
DISC2-15030	Chemically engineered photoreceptors for vision restoration in retinal degeneration associated blindness.	**$1,873,700**	**N**	**83**	82	2	80	84	0	14	Y	N	
DISC2-14943	Conversion of Glioblastoma into Induced Dendritic Cells as a Novel Immunotherapy using Custom-designed HSV Vectors	**$2,240,642**	**N**	**81**	81	5	70	90	4	11	N	N	
DISC2-14915	An integrated microphysiological system to interrogate obesity-associated cardiac disease	**$807,000**	**N**	**81**	81	5	70	93	3	11	N	Y	
DISC2-15164	Oral mRNA-based gene therapy to treat Microvillus Inclusion Disease	**$1,498,637**	**N**	**80**	80	6	70	90	4	11	N	N	
DISC2-15113	Self-delivery of a tissue-targeting CRISPR-Cas9 fusion protein therapeutic for the treatment of a rare liver disease	**$2,003,805**	**N**	**80**	79	7	65	85	4	11	N	N	
DISC2-14890	Transplantation of excitatory V2a interneurons to promote motor function recovery after spinal cord injury	**$1,754,749**	**N**	**80**	79	3	70	80	0	14	N	Y	
DISC2-14937	Optimizing stem cell-derived pancreatic beta cells with parathyroid-inspired supportive niche	**$2,764,200**	**N**	**80**	78	5	70	85	3	12	N	Y	
DISC2-14975	Pluripotent stem cell-derived liver organoids for treatment of liver disease	**$2,764,201**	**N**	**80**	77	4	70	82	0	15	N	N	
DISC2-14902	In vivo engineering of immune cells for cancer therapy	**$2,361,860**	**N**	**80**	76	10	50	85	2	13	N	N	
DISC2-15048	Engineering tunable biomimetic adhesive hydrogel to deliver and enhance MSCs function for corneal regeneration.	**$1,998,474**	**N**	**80**	76	7	62	84	0	15	N	N	
DISC2-15147	Treating Limbal Stem Cell Deficiency with Induced Pluripotent Stem Cells	**$2,311,200**	**N**	**78**	76	3	70	80	0	15	N	N	

APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Resubmission	Previous CIRM Funding	Area of Impact
DISC2-15070	Development of next-generation human cerebellar organoids to model hereditary cerebellar ataxias	**$838,710**	**N**	**77**	77	2	75	80	0	14	Y	N	
DISC2-15155	Self-delivery of a tissue-targeting CRISPR-Cas9 protein-based therapeutic for the treatment of kidney disease	**$1,994,848**	**N**	**75**	76	2	70	80	0	14	N	N	
DISC2-15145	A small molecule therapeutic to differentiate cancer stem cells	**$2,376,000**	**N**	**75**	73	3	70	79	0	15	Y	N	
DISC2-15072	Functional chemical screens in human iPSC-derived cardiomyocytes to identify new cardioprotective drugs	**$813,000**	**N**	**75**	72	4	65	75	0	15	Y	N	
DISC2-14886	Development of spinal cord tissue using human spinal cord stem cells and 3D-printed drug-delivery scaffolds for acute spinal cord injury repair	**$2,232,190**	**N**	**74**	73	4	65	85	1	14	N	N	
DISC2-15020	A Novel, Injectable, and Biodegradable Thermoresponsive Hydrogel for Improved Engraftment and Efficacy of Cell Therapy for Parkinson's Disease	**$1,482,500**	**N**	**72**	73	3	70	79	0	14	Y	Y	
DISC2-14938	The implantable Bioartificial Pancreas (iBAP)	**$2,719,424**	**N**	**70**	72	7	65	85	1	14	N	N	
DISC2-14892	Allogeneic Stem Cell-Engineered CAR-NKT Cells Targeting CD70 for AML Therapy	**$2,364,000**	**N**	**70**	71	5	65	80	0	14	N	Y	
DISC2-14893	A novel bioinformatic strategy to generate cervical V2a interneurons for SCI engraftment	**$2,376,000**	**N**	**70**	71	2	70	79	0	15	N	N	
DISC2-15008	Off-the-shelf stem cell (SC)-derived, hypoimmunogenic "synthetic islets" for reversal of diabetes	**$2,263,502**	**N**	**70**	71	3	70	80	0	15	N	N	
DISC2-14977	An immunoprotective bioreactor for stem cell-derived renal tubule cells enabling an implanted bioartificial kidney	**$631,250**	**N**	**70**	70	5	65	85	1	13	N	N	
DISC2-14905	Stem Cell-Derived Exosomes with Focused Ultrasound for Treatment of Chemotherapy-Induced Brain Toxicity	**$2,240,088**	**N**	**70**	70	4	65	78	0	14	N	N	

APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Resubmission	Previous CIRM Funding	Area of Impact
DISC2-15004	A novel cell therapy product that enables engraftment in a minimally invasive site for patients with type 1 diabetes	**$2,288,000**	**N**	**70**	70	7	60	80	0	15	N	Y	
DISC2-15009	Reprogramming Autologous Brain Tumor-Infiltrating T Cells to a Stem-Like State for Adoptive Cell Therapy (ACT) Using Immune Competent Organoids	**$1,887,752**	**N**	**65**	65	4	60	78	0	12	N	N	
DISC2-15057	Identifying Drugs to Amplify Neural Recovery in Combination with NSCs after SCI	**$2,255,315**	**N**	**65**	65	3	60	70	0	14	N	Y	
DISC2-15174	Immunotherapy for glioblastoma utilizing glioblastoma-targeted microglia derived from human induced pluripotent stem cells (GBT-hiPSC-MG)	**$1,820,984**	**N**	**-**	**-**	**-**	**-**	**-**	0	15	N	N	

*** Minority Report**

Application #	DISC2-14935
Title (as written by the applicant)	Orthogonal IL2 Receptor Transduced Regulatory T Cells for Clinical Application
Research Objective (as written by the applicant)	Genetically modified cells that help control immune reactions
Impact (as written by the applicant)	Improved treatment for patients undergoing transplantation
Major Proposed Activities (as written by the applicant)	• To identify the optimal source of regulatory T cells for introduction of the novel IL2 receptor • To test the impact of a novel IL2 protein on activating the regulatory T cells • To determine the optimal dose and schedule of the novel IL2 protein to expand the regulatory T cells in preclinical models • To test whether the optimal cell product has enhanced function in controlling disease.
Statement of Benefit to California (as written by the applicant)	Many Californians suffer from diseases where transplantation of blood forming stem cells or solid organs are required. Despite success many challenges persist that can be addressed by developing a better strategy to control tissue rejection. This project if successful will set the stage for clinical testing that could aid many patients in California and worldwide.
Funds Requested	$1,920,652
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: 93

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	93
Median	93
Standard Deviation	5
Highest	100
Lowest	85
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 14	• The proposed technology will likely result in a therapeutic candidate that will have a major and lasting impact on prevention of Graft-vs-Host-Disease (GVHD) and possibly many other unmet medical needs such as organ transplantation and autoimmune diseases. • The preliminary data are compelling and very supportive of the proposed project. Applicants have demonstrated that they can activate and expand murine Tregs using their proposed strategy and that this resulted in strongly improved GVHD control and survival of heart transplant in mice. These results provide strong rationale for the proposed testing of the same strategy with human Tregs. • The applicants presented a clear and feasible plan for progression from successful candidate discovery to the initial in vitro studies with human Tregs to in vivo studies in a xeno-GVHD model and to selection of a lead candidate for clinical translation. • Yes, the application proposes to use Tregs derived from cord blood or PBMC in a patient population receiving allogeneic stem cell transplantation (and in the future, other autoimmune diseases or organ transplantation). • In addition to the impact on GVHD, this proposal has scientific impact in determining the best source of Tregs (GCSF-mobilized peripheral blood mononuclear cells [PBMCs] versus cord blood) and processeses for freeze/thawing. Being able to genetically mark the Tregs, and give them orthogonal IL-2 is also exciting. • Yes, the applicants present a very thoughtful rationale, process, and progression. They have prior clinical experience in translation, and access to critical reagents is provided.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• The scientific rationale for this study is exceptionally strong. The role of Tregs in controlling GVHD is well established, in part due to pioneering contributions from the applicants. It's also well established that the inability to selectively activate and expand Treg for clinical use is a major bottleneck in the filed that is addressed in the proposed study. • The proposed project is uniquely enabling for the advancement of stem cell-based and genetic therapies. • Yes. Tregs have been highly promising in principle but challenging in practice for a variety of reasons (low numbers, low persistence, hard to freeze/thaw, hard to track, hard to support with drugs in vivo to enhance activity). This proposal actually addresses mechanisms to overcome all of these challenges in a very systematic and progressive way. • Yes, there are preliminary data in multiple transplantation models that show benefit. Moreover, the investigators are critical of their own data and thoughtfully discuss trends and implications. • Yes, the team has clear clinical experience and the application is well written.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 14	• The project is meticulously planned with excellent descriptions of goals and expected outcomes. There are strong proof-of-concept data including in murine Treg models and the initial testing of the proposed IL-2 expression system in a phase 1 clinical trial with CAR-T cells. • The project plan and timeline demonstrate an urgency that is commensurate with CIRM's mission. It's very likely that at the end of this project, a clearly defined cellular product will be ready for an IND application. • The research plan is exceedingly well planned and proposed, describing and systematically overcoming multiple challenges. • The planning is systematic regarding addressing potential pitfalls and alternative approaches. • Applicants paid attention to both conceptual and technical pitfalls and provided logical alternative approaches. • The applicants outline approaches/considerations for safety and toxicity. • This an exceptionally well-constructed, exemplary project. • This is a very well constructed and promising project.

	• The application demonstrates excellent grantwriting in that it goes deep into clinical experience, almost as if one is reading a text book written just for this proposal (via the discussion of the history of challenges of transplant, GVHD, and Treg mechanisms and promise, with a hard look at the challenges), while at the same time providing experimental details down to cell numbers, transduction, and culture methods. • Yes, and the applicants already have an open IND for other clinical studies with Treg therapies. • The applicants do not specify all animal models proposed, and some descriptions of in vivo experiments lack details such as timeframe of treatment and cell number.
No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 14	• The proposed milestones and expected project outcome are logical and likely to be achieved within the proposed timeline. • The teams from the collaborating institutions are the leaders in the field and are exceptionally well qualified for this project. • The applicants are a dual institution team, each with experience and qualifications and synergy. • The teams have developed all required models and tools for this projects in their labs and have secured outstanding resources from their institutions. • The applicants have access to critical reagents from • The budget is appropriate. • Yes, in part because the applicants already have access to critical reagents from a California-based cytokine therapeutics company. • The applicants have not addressed how they will scale up their therapy for the clinic.
No: 0	*none*
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 14	• The project plan and design adequately address and account for the influence of race, ethnicity, sex and gender diversity. • The application has a strong DEI component, as the proposed approach could make transplant more feasible for larger numbers of diverse patients who currently may not be able to access transplant due to only having 7 out of 8 HLA allele matches, and for whom GVHD risk is high. The applicants provide actual percentages of eligible patients from different groups. • The applicants discuss HLAs and include a well developed DEI statement. • Yes, the project outcomes inform the development of a product or tool that serves the unmet medical needs of the diverse California population, including underserved racial/ethnic communities. • The applicants do incorporate perspectives and experience from the population that will benefit from the proposed product in the implementation of the research project, although this is in the early stage of a discovery project.
No: 0	*none*

Application #	DISC2-15120
Title (as written by the applicant)	Gene-corrected human microglia for the treatment of adult onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP)
Research Objective (as written by the applicant)	The research proposed here will support the development a cell therapy for treating adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP).
Impact (as written by the applicant)	Successful development of the gene-corrected cel therapy will result in a life-altering therapy for patients suffering from ALSP and provide proof of concept for treating other microglia diseases.
Major Proposed Activities (as written by the applicant)	• Demonstrate the in vitro safety and efficacy of gene corrected iPSC-derived microglia. • Demonstrate preclinical efficacy and safety of gene corrected iPSC-derived microglia.
Statement of Benefit to California (as written by the applicant)	The applicant organization and two primary contractors are California-based. Funding of this work will provide direct economic benefit to these organizations in addition to providing needed therapies to California citizens suffering from microglia diseases.
Funds Requested	$1,417,948
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	4
Highest	97
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 project hold the necessary significance and potential for impact?
Yes: 15	• The absence of a cure or therapeutic intervention for adult-onset encephalopathy with axonal spheroids and pigmented glia (ALSP), a primary microgliopathy, is presently

	evident, resulting in a substantial impact on numerous individuals within the United States. • ALSP is a rare disease with no disease modifying therapies available, thus the proposal addresses an unmet need. • The proposal is for a therapy that is potentially curative. Although it may need to be reintroduced every few years, it has essentially no competition with anything near that level of efficacy, so it's very much meeting a need. Fixing a single defective gene which is completely responsible for a severe disease phenotype is the classic application of stem cell therapy, so this very much in line with leveraging stem cells for therapy. • The goal of the project is a candidate therapeutic ready for IND-enabling studies. • The applicants have had meetings with the FDA and present a plan for taking the steps needed for clinical development. • The applicants have a well thought-out set of transitions, as well as extensive safety protocols, which will become even more important as they shift to human work. • The application is targeting a micropathology in the brain caused by a well defined mutation in a specific gene.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 15	• The proposal presents an alternative approach to bone marrow transplantation/ hematopoietic stem cell transplantation for dysfunctional microglia by using microglia derived from human iPSC. Since human microglia cannot be isolated in sufficient quantities for such therapies, investigating new sources of cells makes sense. • Human microglia are hard to obtain in high numbers, so the use of iPSCs as a starting source makes sense. • The applicants have developed novel tools and have FDA feedback on their approach to treating this rare disease. • The level of preliminary data is excellent, and there is a clear development path incorporating FDA input. • The rationale is straightforward: a genetic defect causes the disease, and simply replacing the gene should fix the disease progression (although it is unclear if prior symptoms will improve, but it could be possible). The applicants have data on their ability to generate edited cells, and transplant them to rescue the phenotype in a mouse model, all supporting this rationale. • Data in the mouse model is very convincing, as this model has the same genetic mutation as the human disease and and microglial cell therapy works in this model phenotypically. • The required in vitro and in vivo assays were established to authenticate the functional activity, biological activity, and safety of engrafted induced microglia-like cells (iMGL) derived from healthy human cell lines. • The project is based on previous work, as evidenced by preliminary data presented in proposal.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 15	• This application is right on the cusp of human studies, as the applicants are transplanting edited human cells into a mouse model. This project has clearly been considered from multiple angles by a PI with a lot of experience designing related projects. A range of outcomes and possible alternative approaches are considered. • The project is well planned and designed and ready to advance. • The project aims to provide evidence of the preclinical efficacy and safety of gene-corrected induced macrophage-like cells (iMGL). The approach taken is comprehensive; however, it is lacking in terms of the number of cell lines utilized. • The project is generally well designed, but microglia generated using the protocol provided by the applicants have not been sufficiently compared to microglia generated using other iPSC-based protocols.

	• One question regarding the design concerns the placement of grafts in the animal model versus in the clinic. In the clinic, the cells will be placed in the cortex but in mouse they are placed in the hippocampus with the argument that is is experimentally easier. However, the hippocampus is a neurogenic environment while the cortex is not, and no data are provided to support that the outcomes will be the same in a neurogenic vs non-neurogenic niche.
No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 15	• The progress these applicants have made so far indicate that the work is feasible. • The applicant team is strong and has relevant expertise. • All necessary resources are in place. • The budget is well justified. • The applicants have prior FDA interaction and feedback, and a path forward. • The application team is composed of highly regarded, talented, and committed scientists. • It is concerning that animal models study transplantation in the hippocampus, and how this would relate to feasibility of transplant in the cortex in humans.
No: 0	*none*
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 15	• The experimental systems takes DEI into account. The applicants plan to use blood from five registrants to capture the diversity of the California population of ALSP patients. It is a rare disease and this seems sufficient. • There will be significant proportion of minority individuals treated in the project. It would be encouraging to see a provision made that those who donate cells at this stage are ensured a slot in human trials. Given that the variant tested is not confined to a particular group, and their intentional, professional outreach to underserved groups, there is a very strong likelihood that the treatment would ultimately benefit communities with unmet needs. • The applicant has engaged with the ALSP community in several ways including sponsoring (with CIRM) the first ALSP conference attended by patients and caregivers and providing funding for an LSP patient registry. • The applicants have already had strong integrations with patient registries, outreach, testing, and counseling. The applicants also take into consideration patients' wishes to have data they contribute be shared.
No: 0	*none*

Application #	DISC2-15119
Title (as written by the applicant)	Drug discovery for gastrointestinal motility disorders using hPSC-derived enteric ganglioids
Research Objective (as written by the applicant)	Our goal is to use stem cell models to identify a small molecule drug candidate for GI motility disorders.
Impact (as written by the applicant)	The candidate will be used for severe gastrointestinal motility disorders including chronic constipation, achalasia and gastroparesis.
Major Proposed Activities (as written by the applicant)	• Assessment of candidate compounds on stem cell derived models from diverse genetic backgrounds • Evaluation of effectiveness on mouse tissue • Understanding the underlying therapeutic effect of the drug candidates • Identification of the best performing drug candidate for follow-up assessment in animal models • Evaluation of safety and dosing regimen in animal models • Testing the effectiveness of drug candidate in animal models
Statement of Benefit to California (as written by the applicant)	Gastrointestinal motility disorders are highly common and affect a large patient population in California. Currently available treatment options are limited and ineffective leading to reduced quality of life and increased burden of care.
Funds Requested	$1,954,367
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	88
Lowest	80
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 project hold the necessary significance and potential for impact?
Yes: 15	• The applicant clearly identifies that GI dysmotility disorders affect a significant portion of the population, making it a pressing issue that warrants investigation. • If successful, the candidates could be used for severe gastrointestinal motility disorders including chronic constipation, achalasia, and gastroparesis. • The application addresses unmet need in an area that is not top of mind for research and is an area of study that can make a difference in therapeutic discovery. • The proposal provides a comprehensive understanding of the enteric nervous system, emphasizing the specific role of NO neurons and their potential as therapeutic targets. • The proposed research covers a broad spectrum, from compound identification to in vivo testing, offering a complete pathway from lab-based research to potential clinical application. • The applicants present a very innovative and unique approach. • This application is stage-appropriate for Quest, and the applicants provide a thoughtful progression toward clinical trials. • The applicant has already conducted preliminary studies and found potential NO modulators. This suggests that they are building upon existing work, indicating a higher probability of success. • The research plan aims to test hit compounds on hiPSC lines from various racial and ethnic backgrounds, which can improve the generalizability and inclusivity of the research results. • The applicants make good use of in vitro iPSC derived platforms and in vivo screens. • The use of enteric ganglioids is presented as a novel and scalable method to study the human ENS, potentially overcoming limitations faced in traditional research methods. • While enteric ganglioids present a solution to some scalability issues, large-scale production and maintenance of these models might come with its own set of challenges. • The complexity and interconnected nature of the ENS might pose challenges, even with the new model. Not all aspects of human physiology may be recapitulated in the enteric ganglioid model. • The grant seems heavily focused on enteric NO neurons. While these are evidently significant, the ENS and GI dysmotility may have other crucial aspects that are not addressed. • While the proposal mentions in vivo testing for toxicity, there could be unforeseen side effects when modulating neuronal activity, which might not be evident in the short-term studies proposed. • The proposal does not explicitly address how long the identified compounds would provide relief or if they address the root causes of disorders of gut-brain interactions or just the symptoms. • It is unknown whether this screening would be medically efficacious.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• There's a significant lack of comprehensive knowledge about human NO neurons due to challenges in accessing the primary ENS tissue for study. This gap necessitates innovative methods to study these neurons in depth. • Since the dysfunction of NO neurons is tied to many GI motility disorders, enhancing their activity could be a promising therapeutic strategy. • The application includes strong preliminary data demonstrating cell targeting and mechanism of action in ENS neurons. • Strong in vitro and in vivo data are included in humans and animal models.
No: 2	• The proposed screening is ambitious while missing key proof of concept in vivo data, ultimately limiting translatability. • Yes, but this is an early stage proposal. • Yes, but the research is high risk and high reward. • Data demonstrating that increasing NO from ENS cultures reflects parallel improved function in vivo would be needed to strengthen the proposal's clinical potential.
GWG Votes	**Is the project well planned and designed?**

Yes:
15
	• The research aims provides contingencies for potential challenges, demonstrating a well-thought-out strategy.
	• The application includes well-developed pitfalls and alternative strategies.
	• The use of single cell transcriptomics datasets of hPSC-derived ENS cultures offers precision and granularity, which can provide a deeper understanding of target expression in NO neurons and other enteric neuron subtypes.
	• Employing CRISPRi will aid in identifying drug targets, and the subsequent validation with qPCR, western blots, and flow cytometry further establishes the robustness of this approach.
	  • Acknowledging that some drugs might stimulate NO neurons through multiple protein targets shows an understanding of the complexity of drug actions. Testing for potential synergistic effects when multiple targets are implicated is a thoughtful approach.
	  • A backup plan to use siRNA mediated knockdown if Cas9/gRNA RNPs yield low knockout efficiencies provides a safety net, ensuring project continuity.
	  • The focus on specific compounds like aripiprazole and brexpiprazole, while illustrative, might limit the broader applicability or insights into other potential compounds.
	  • The applicants could further consider mosaicism in these approaches.
	• Using cell lines from both male and female donors of different racial backgrounds increases the potential applicability and relevance of results.
	• Multiple diverse lines are included, which will broaden the evaluation of identified targets in the first step.
	• Utilizing different methods and assays of gut function provides a comprehensive analysis of the neuronal responses.
	• The applicants present a thoughtful progression from filtered identification to validation in vivo with animal models.
	• The procedure adopts a stepwise narrowing down from 37 compounds to 10 and then to 5 based on various criteria, ensuring that only the most promising candidates progress.
	• Given the preliminary data and the careful design, the project seems feasible
	• The project is very ambitious and missing some key proof of concept data that would be important to support the translational potential of this screening approach.
	• The approach is heavily based on the success of previously identified molecules. If these molecules turn out to be less effective than anticipated, the entire strategy may need reevaluation.
	• Using multiple hiPSC lines could introduce variability in results, which might complicate reproducibility of data analysis by the same team at a later stage or by a different team.
	• A negative screen against other types of neurons may be used to avoid compounds that have off-target effects on other cell types.
	• The order of the screens could be modified.

No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 14	• The applicant's team has established a new method to study the human ENS using human pluripotent stem cell (hPSC) differentiation. Their work showed that both 2D ENS cultures and 3D enteric ganglioids closely mimic the natural human ENS, providing a reliable model for further research. • In their earlier studies, they've created a differentiation strategy to enrich for NO neurons in their hPSC-derived ENS cultures. This advancement sets the stage for targeted research on these critical neurons. • Using their developed system, they successfully conducted a screen and identified compounds that could enhance the activity of NO neurons and promote the release of NO. This indicates they're not starting from scratch and are building on established results. • Their previous findings, as outlined in the study under revision, form the basis for the current grant application. They aim to leverage their findings and models to advance therapeutic candidates for DGBIs. • The application is from a strong team with good momentum on this project. • A robust system for validation is available.

	• The approach involves a complex mix of cells, which can make identifying candidate cell lines or therapies a challenge. • This is a high risk and high reward proposal. Is the screening method truly a viable option for candidate cell selection in a complex organoid system?
No: 0	*none*
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 14	• Yes - the work proposes to use a diverse panel of hiPSC lines from different racial and ethnic backgrounds (obtained from the CIRM repository). • DEI is addressed by the use of multiple cell lines. • The applicant will use some experiences in their institution's graduate program DEI committee to guide their research.
No: 0	*none*

Application #	DISC2-14982
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)	Use of a viral vector to transport a normal gene to children with severe motor and respiratory disabilities caused by an inborn defect of the choline acetyltransferase (ChAT) gene.
Impact (as written by the applicant)	Treatment of an incurable disease in infants and potential amelioration of symptoms of neurodegenerative diseases with deficient cholinergic system such as Alzheimer and Parkinson disease.
Major Proposed Activities (as written by the applicant)	• Refining the development of an AAV vector carrying the human ChAT gene and transducing normal human induced pluripotent stem cells (iPSCs) with this vector to demonstrate effective transduction. • Transducing iPSCs derived from affected patients and demonstrating recovery of normal ChAT function by an enzymatic potency assay. • Injection of the AAV virus transporting the human ChAT gene into mice that are deficient of this gene and testing the survival and motor strength of injected and non-injected mice • Immunohistochemistry to measure the expression of choline acetyltransferase in the central nervous system of AAV-treated and non-treated mice. • Quantitation of vector copies and RNA expression of the ChAT gene in the nervous system and peripheral organs using real time PCR. • Histologic analysis of brain and peripheral tissues of long-surviving mice injected with the AAV vector to verify the absence of long term adverse effects.
Statement of Benefit to California (as written by the applicant)	• Deficiency of ChAT affects all racial groups but is common in Native American and Asians which are two important ethnic groups of the State of California. • Current treatments for deficiency of choline acetyltransferase are ineffective and the ancillary services (care of tracheotomy, mechanical ventilation, and gastric tubes) are very onerous for the State of California. • The development of this novel gene therapy locally will provide jobs and financial growth for the State of California.
Funds Requested	$1,500,000
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 86

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

Mean	84
Median	86
Standard Deviation	5
Highest	90
Lowest	75
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	9
(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 project hold the necessary significance and potential for impact?
Yes: 15	• This application is focused on providing gene therapy for Congenital Myasthenic Syndromes (CMS), defined by congenital deficient forms of the enzyme ChAT leading to a deficit in acetylcholine at the motor nerve terminals of the neuromuscular junction. The disease is often fatal and there is currently no therapeutic approach. • Development of a genetic therapy for CMS caused by ChAT deficiency would improve patient care for this population. The therapy methodology also could be applied for treatment of several other presynaptic variants of CMS in which the defective gene is translated in the spinal motor neuron (SMN). • The disease is a good candidate for AAV9-based gene therapy. Such a therapy would be a "game changer" to these patients. • The approach is potentially curative and would only require one intervention. Current pharmacologic treatments show low efficacy and have severe side effects. • The approach here could provide a roadmap for other presynaptic variants of CMS that present with severe disease. Spinal motor neurons are a suitable target for CMS and AAV based approaches (Zolgensma) to target these specific cells have already been approved by the FDA for treatment of a neurologic disorder. Thus the potential for clinical translation is high. • The study aims to address a notable gap in medical care by focusing on a particular variant of CMS that is associated with elevated rates of mortality and impairment, as well as limited response to standard therapeutic approaches. • The specific models of a ChAT mutation used in this application is one of the more common forms of CMS, which is generally very rare. A therapeutic agent targeting this form would thus have the highest impact. • This would be a life saving therapy for patients.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 15	• The applicant shows interesting data about the efficiency of the AAV-ChAT construct: animals with mutant ChAT injected prior to pathology show increased survival probability, increased ChAT expression in spinal cords, and normal motor function while non-injected animals develop disease and and die prematurely. • The vector used in this application is already known to bypass the blood brain barrier and to preferentially transduce spinal motor neurons. The promoter that is used has been shown to provide strong, long-term, and ubiquitous central nervous system (CNS) expression, thus increasing the possibility for success. • The selection of the AAV9 vector as a carrier is justified by its demonstrated efficacy in transducing SMNs, which play a crucial role in the pathogenesis of the disease. • The inducible mouse models allow for postnatal intervention, and mice show many hallmarks of the human disease despite CNS-wide ChAT knockout (generally, incomplete excision and extremely high demand for ChAT in SMNs renders these cells highly vulnerable) • The approach proposed here has been FDA cleared and approved for another disease. • A strength of this proposal is that the applicants have already demonstrated proof of concept, and are now working backwards trying to determine why the therapy is working. • This project is a resubmission of an earlier application that was criticized on the grounds that the preliminary experiments were not conducted on animals that would be relevant to the human condition. The applicants explained that the timing of treatment was chosen on the basis of trying to optimize the two parameters of survival and motor impairment. • The proof of concept data that used a non-clinical relevant injection scheme was followed by a clinical relevant pilot study where animals with mutant ChAT receive the AAV-ChAT construct after the onset of pathology and are followed until postnatal week 12. In this

	scheme, the applicants report increased survival of treated animals relative to untreated animals. This is an exciting progression of the project. • Preliminary immunohistochemistry shows increased ChAT expression after AAV-ChAT at post-natal day 28, but the timepoint of the labeling is not clear. • An appropriate mouse model has been constructed, and is suitable for initial experiments. They are also working on an alternative approach that targets models of human mutations. • A methodology of this nature is of critical importance for the management of CMS because it represents the first attempt to achieve a curative therapy for deficiency of ChAT. • The proposed experiments appear to be feasible and efficacious for improving motor function and preventing death. • The rational of Milestone 2 is to generate a product with high transduction efficiency in human neurons. However, the applicant provides a generic protocol for generating neuronal precursor cells from iPSC that will then be transduced with AAV-ChAT . It is not clear how efficiency in neuronal precursor cells is related to efficiency of transduction of differentiated SMNs that are the ultimate in vivo target. • It is not clear how ChAT levels in neuronal precursor cells relate to ChAT levels in differentiated SMNs.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 13	• The applicant has now included preliminary data using a clinically relevant injection scheme that shows some promising results. While the analysis was limited to survival with no additional data on disease modulations, the data are exciting. • The project milestones are appropriate for the preclinical analysis of the proposed therapeutic agent. • The discussion of pitfalls is limited to experimental procedures. The applicants do not discuss alternative outcomes or unexpected results. For example, the experiment in milestone 3 might show a partial rescue of some defects or might show recovery to a percentage of wild-type ChAT functional levels. If this is the case, would the milestone be considered not successful? • The mouse model originally used for early efficacy was a global ChAT knockout, which was not a true disease model given the target age for gene therapy. Now, the applicants are using a model that develops disease later in development which is more clinically relevant. • The project has been somewhat derisked, as the applicants can utilize much of the toxicity data available for an approved product using a similar vector. • Milestone 2 is poorly developed and incomplete as NPC are not further differentiated into neurons to show sustained ChAT activity.
No: 2	*none*
GWG Votes	**Is the project feasible?**
Yes: 15	• This is a well constructed project, with appropriate analysis of clinically relevant endpoints and of potential toxicities. • The mouse data support feasibility. • Preliminary data support overall feasibility. • The project is feasible because there is a precedent pathway for this approach, based on an FDA cleared product in a different disease. • The optimal or target timepoint for treating patients is unclear. • There is no discussion on potential challenges for scaling the product to treat human disease. • Milestone 2 requires biopsies from patients and subsequent iPSC production from fibroblasts. While a relevant IRB protocol exists for a different disease, it is not clear whether patients have been recruited for generating the required biopsy samples.
No: 0	*none*
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**

Yes: 15	• The discussion about providing a therapeutic approach for a rare mutation in Native Americas is excellent. • One-third of the families in the previous studies belong to Native American and Asian groups, and two-thirds of the patients were females. • Appropriate attention has been paid to working with patients from minority populations. • The DEI efforts are inadequate in respect to sex. Experiments included both male and female subjects but data are only shown for combined cohorts, with bar diagrams without individual points. Averaging the weights of males and females in a cohort of adult animals post weaning seems inappropriate and should in fact led to more variation. • Exclusion of sex a a variable is premature based on the low power of data shown in Figure 5. There is no consideration of gender in the generation of IPSC derived cells.
No: 0	*none*

Application #	DISC2-15010
Title (as written by the applicant)	C9orf72 repeat expansion-tuned allelic suppression by CRISPRi as an ALS therapy
Research Objective (as written by the applicant)	We aim to discover an adeno-associated viral (AAV) CRISPRi gene therapy for amyotrophic lateral sclerosis (ALS) patients with hexanucleotide repeat expansions in the C9orf72 gene.
Impact (as written by the applicant)	This therapy can be administered intravenously once, have long lasting effects, and is indicated for all ALS patients who carry repeat expansions of varying lengths and toxicity in the C9orf72 gene.
Major Proposed Activities (as written by the applicant)	• Establish a high-throughput cellular platform to screen for an optimized small guide RNA (sgRNA) and CRISPRi system that selectively silences long, pathogenic C9orf72 repeat expansions. • Generate neural cells from C9orf72 ALS patient induced pluripotent stem cells (iPSCs) and optimize the AAV CRISPRi system to reduce toxic RNA and protein products caused by C9orf72 repeat expansions. • Test the reproducibility of the AAV CRISPRi system to reduce toxic RNA and protein products in iPSC models of 15 female and 15 male C9orf72 ALS patients while assessing any off-target genomic effects. • Optimize the AAV CRISPRi therapy in mice genetically modified with pathogenic C9orf72 repeat expansions and test its ability to reduce toxic RNA and protein products while preserving motor function.
Statement of Benefit to California (as written by the applicant)	ALS currently affects thousands of Californians with no cure. Patients rely on full-time caregivers, and underserved communities have a disproportionate burden. We use a rational combination of technologies to treat this genetic form of ALS caused by DNA repeat expansions. If we are successful, our approach can readily transfer to other repeat expansion diseases in neurodegeneration. This would markedly alleviate the neurodegenerative disease risks facing a rapidly aging California population.
Funds Requested	$2,274,768
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	5
Highest	92
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	13
(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 project hold the necessary significance and potential for impact?
Yes: 15	• The project aims to develop a CRISPRi based strategy targeting C9orf72 repeat expansion. This is relevant for a familial ALS patients with this mutation. There are currently no treatments or cures for ALS and this project addresses an unmet need. • Primarily for ALS but also potentially for frontotemporal dementia. Strategy of short guideRNAs for allele-specificity can also be relevant for other repeat disorders. • ALS requires new treatment strategies, and the proposal articulates an interesting and novel approach to do so. • This is a severe disease that's never had any substantial therapies despite many tries. • After completion, the applicants plan to apply for a TRAN1 award to conduct preclinical development stage activities towards initiating IND studies. • Concerns were raised but this is critical unmet medical need... high risk, high reward. • It is likely, but in the 55/45 sense of likely.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 15	• The project has a clear and obvious rationale to selectively target pathological C9orf72. What makes this approach slightly different from others is the design to minimize the interference at the healthy C9orf72 allele. • Allele-specific CRISPRi is well-supported by preliminary data and the sequence of experiments is sensible. • Allele specific targeting makes sense. • Preliminary data is supplied that supports the strategy for selective bias to targeting and silencing alleles with more repeats. The preliminary data also shows that this is competitive compared to introducing mismatched nucleotides in full length guides that would be an alternative approach. • 30 ALS patient and 10 healthy control iPSC lines will be acquired from a stem cell core repository. They will be differentiated/directed to motor neurons and microglia according to published protocols, but there is no preliminary data on how effective this is across the lines. • Perhaps too many tests, not taking into account the cell line variability. • There's a clear causal link between repeat expansion (which this therapy addresses) in this and related diseases. The crux of the project is allele-specific sgRNA/Cas binding, and they do show that this happens, so that's promising, although I'm seeing 50% reduction in the disease allele and it is not clear (or tested here) if that's enough to have a meaningful phenotypic effect. • Can we achieve enough silencing with the alleles? • Will there be enough delivery? Enough knockdown? A single vector is a risk and it is unclear if they can get into cells with enough efficiency. • Can they design the vector and do the cell models work?
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 14	• There is a clear and logical flow of testing through to animal models. • The proposal is very well-written and illustrated. • The approach of starting in HEK cells and moving into patient-derived cells and then animal models is reasonable and likely to provide useful data, even if the approach is not successful. • The project is in general well designed but early in its phase. It starts with establishment of a high-throughput cellular screening platform with a dual reporter system that will be used to screen for optimized sgRNA candidates that selectively silence long, pathogenic

	C9orf72 repeat expansions. This will be followed by testing candidates in iPSC-based cell models and efficacy in vivo using transgenic mouse models. • Strategies for eliminating the impact of off-target effects in place. • The team has expertise. • There will be a Cas-based strategy for targeting ALS specifically and repeat expansion diseases more generally at the end of this project, which would be ready for translational studies if they succeed. • There is a risk that no candidates with strong enough effect are identified in the initial screen and this pose a risk to the project. • The contingency plan for iPSC-based modelling is direct conversion to generate iMNs and iMGs. This approach bypasses the need for the multi-stage differentiation process and significantly shortens the overall duration of the protocol, but it is risky, could take a long time to develop and may not work. • Although switching to dCas13 would be more of a pivot than an alternative approach, in general they identified the next most logical approach to try if the primary fails. • Some concerns about the lack of important preliminary data.
No: 1	• Delivery of the guide is much easier than delivering the entire editor. That work should be given more time and effort in the proposal.
GWG Votes	**Is the project feasible?**
Yes: 13	• There's strong experience in ALS, stem cells and genomic engineering, so all the bases are covered. • The proposed milestones are feasible provided that the screen yields candidates and provided that the iPSC system can be used. • The team contains expertise with human iPSC-based models of neurodegeneration as well as CRISPR based screens. • Could be added to already available therapies in the clinic. • The success of the application all comes down to whether you can get relative suppression of the disease allele via more frequent binding of the repressor domains in the repeat region. Everything else is organized around tuning the guides to make this happen and checking phenotypic outputs. All of the activity/milestones are organized around this goal and reasonably feasible to achieve, given the overall difficulty of making progress on this disease. • While it is conceivable that the approach will work, the major concern was about the ability of the applicants to deliver sufficient amount of the CRISPRi vector via AAV to a sufficient number of cells and achieve a sufficient amount of allele-specific knockdown to have therapeutic benefit. The packaging capacity of AAV for an all-in-one CRISPR vector is a major concern. However, AAV technology is steadily increasing and options such as intrathecal delivery could improve delivery efficiency. • Concerns about a long term therapeutic effect. • High risk in the packaging and delivery. This is acknowledged by applicants but would need some preliminary data. • I would strongly recommend that when applicants test AAV delivery via a GFP-expressing virus, that the viral genome size be artificially increased to match that of the CRISPRi vector to more closely match their therapeutic vector.
No: 2	• Delivery is a significant pitfall that is not well considered. • Some concerns about level of efficacy that can be achieved.
GWG Votes	Does the project uphold principles of diversity, equity and inclusion (DEI)?
Yes: 15	• The iPSC lines to be used will be sex balanced but the diversity unclear. Female and male genotypes are included in all experiments. • Diverse set of genetic backgrounds will be used. • Sex is clearly considered, and the applicants will use a number of cell lines with different repeat lengths to test their approach. I encourage them to obtain ALS iPSCs from other sources to ensure that genetic diversity is better sampled. • While they discuss racial disparities, all they're actually doing in the study is a balanced male/female origin for their cell lines.
No: 0	*none*

Application #	DISC2-14897
Title (as written by the applicant)	Assessing the Functional, Immunologic and Microbiologic Characteristics of Human Livers Created in Chimeric Pigs
Research Objective (as written by the applicant)	Generating human liver using pig as a bioreactor
Impact (as written by the applicant)	The livers produced will be used for transplantation into patients with end-stage liver disease, metabolic disorders, and for metastatic liver disease not amenable to resection
Major Proposed Activities (as written by the applicant)	• Procure liver from control pig. Place on XVIVO Perfusion Device. • Procure livers from 5 control pigs and 5 modified pigs. Perfuse on XVIVO device for up to 5 days each and collect blood and tissue samples. • Procure livers from 5 additional control pigs and 5 modified pigs. Interim analysis of gross and histologic findings to determine the presence of accelerated and acute rejection. • Procure livers from up to 10 additional control pigs and 10 modified pigs as indicated by preliminary analysis. Complete all blood and tissue collection. • Analysis of all data and statistical comparison of labs, the viability and serologic results. Determine if any additional tests are required utilizing the repository samples. • Completion of all reports, manuscripts and presentations. Preparation of protocols for future studies indicated by results of this study.
Statement of Benefit to California (as written by the applicant)	There is a nationwide shortage of suitable transplant organs and California is one of the most heavily impacted states. California has one of the most profound organ shortages resulting in sicker patients being transplanted with longer hospital stays, more morbidity and impacting mortality. Significantly, Hispanics and minorities are the most disaffected grouping due to late diagnosis and referrals, often resulting in poor prognosis and moving them into high risk bracket for transplantation.
Funds Requested	$2,736,590
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	5
Highest	92
Lowest	77
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 project hold the necessary significance and potential for impact?
Yes: 15	• The proposed technology: production of a humanized liver in a genetically modified pig model for human transplantation is significant and can strongly impact an unmet medical need. • Tremendous unmet need for liver tissue for transplants. • The expected candidate product, together with modifications to the genome of the pig designed to reduce the immunogenicity and eliminate transfer of porcine endogenous retroviruses would increase the likelihood of successfully developing stem cell technology and genetic therapy to improve patient care. • Focus to generate human liver tissue from animals. • Amazing progress in xenotransplantation making three giant leaps- knocking out Porcine endogenous retroviruses (PERVs), establishing human protein production. • Outcome measures of PERV infection, human protein production and immune response tackle all the right issues in liver xenotransplantation. • If successful, might revolutionize liver transplantation and possibly other organs as well. • The identified unmet medical need is the paucity of livers that are available for transplantation into humans. The proposed technology is innovative, timely, important and the proposed technology could result in a candidate product that ultimately impacts that unmet medical need. That said, the project itself is relatively high risk and it is questionable that the technology is likely to result in a candidate that would be ready for translational (human) studies within three years.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• Major strengths is state of the art testing of liver xenotransplant using human blood perfusion. • The company has established expertise in pig knockouts. • Very exciting data showing chimeric livers. • Liver transplant team with many years of truly outstanding experience; leaders in the field of clinical advances and as a consequence have designed a pre-clinical testing program that addresses important issues in translation to clinic. • The preliminary data is robust, well presented and supports the feasibility of each of the milestones. The approach is logical for knocking out the gene responsible for generating pig liver; and rescuing fetuses by embryonic iPSCs. They provide proof of concept validation in generating "anhepatic" pigs and functional rescue with iPSCs. The pigs are also genetically engineered to overcome PERV and hyper- and -acute rejection. • The PI and collaborators hypothesized that the perfusion device which is normally used to maintain procured organs using oxygenated blood, can also be used to demonstrate that the immunologically modified pig liver will not undergo acute rejection when transplanted in vivo, can produce human proteins, and will not carry significant pathogens or porcine retroviruses. This is a reasonable hypothesis but a scientific rationale for it will require additional testing. • The proposed project is based on sound scientific rationale. The use of genetic engineering and blastocyst complementation to create human organs in pigs is cutting edge and a major focus of research in regenerative medicine. Conceptually, the approach is designed to generate livers made up of 100% human hepatocytes. However, they did not address the immunogenicity of pig endothelium in the transplanted "human" liver, which could present a major challenge. • Progression to liver transplantation is not clear.
No: 1	*none*

GWG Votes	Is the project well planned and designed?
Yes: 14	• A significant issue in pig liver transplants noted by bridge use of pig livers is the inability to produce needed coagulation factors; using human tissue for the developing liver completely circumvents this in an elegant way. • This is a well-constructed quality project based on a major unmet medical need. The collaborative institution is a leader in the field of genetic engineering and the use of large animals as bioreactors. Their technology is key and a hallmark of their collaboration with the applicant. The technology at hand could potentially bridge a critical gap in the availability of human livers for transplantation. Strong preliminary data support the feasibility of the project with the potential concerns noted. • Collaborative effort - PI has model and experimental animal expertise partnerships with industry. • Well planned and well designed. They have the preliminary data and have the ability to do the knock out. • Carefully planned with immediate clinical application in mind. • The project is appropriately designed to test whether the blood perfusion device will mimic the in vivo conditions of acute rejection. The project's design is straightforward and logical. Pitfalls and alternative strategies are discussed, but they primarily concern technical issues of how to adopt the perfusion device to pig's anatomy or issues that would need to be solved by the collaborator. • The project is adequately planned and designed to achieve the expected outcome, including proof-of-concept for a candidate product that could potentially advance to human trials. Two major roadblocks exist in the design of the study, including proof of chimeric fetus development to term, and the immunogenicity associated with porcine endothelium within the transplanted liver. This is relevant to issues concerning allogeneic cell components that are almost invariably immunogenic. • Potential problems and alternatives approaches are provided for both Aims. There is, however, no mention of potential problems if the studies are unable to bring the fetuses to term. The study describes control and genetically modified livers, their perfusion and analyses. It is confusing as to whether the genetically modified livers are those only engineered for rejection or the complemented human livers. • No full term liver has been shown. • A significant issue in transplant porcine livers or porcine tissues in general is PERVs and the approach to genetically modify their transmission is impressive; use of culture and not PCR may not be sensitive enough to detect PERVs; target of PERV A and B would be helpful.
No: 1	*none*
GWG Votes	**Is the project feasible?**
Yes: 14	• The PI and the team are outstanding in their expertise and contributions to the project ranging from surgery to basic immunology. In addition, the team at the collaborating institution is highly qualified to generate the "modified" livers based on the use of gene editing and blastocyst complementation, as per the preliminary data. Although the co-Is at the applicant institution are involved at relatively small % efforts, this should not present a problem in generating and analyzing the data as described. • The teams have all the necessary resources, cores, and the like to conduct the proposed activities. The animal core and biostatistical core will be important factors in data production and analyses. In addition, computational resources and specimen processing and shipping are all well-suited for the project. There are absolutely no concerns including shipping of the pigs to California. • The milestones are logical and are likely to be achieved within the proposed timeline. The team is large, and the roles of some of the team members are not clearly outlined. The size of the team appears to be excessive. • Despite beautiful data on fetal chimerism, there was some skepticism regarding the ability to deliver a live pig with the appropriate genes knocked out and this was perceived to be a significant potential obstacle towards feasibility. • The milestones and project outcome are logical. It is a bit unclear, however, as to whether the expected outcome, i.e. that of a "modified" liver is one that has been genetically engineered only to reduce hyperacute and acute rejection or to also bring to full term a

	humanized chimeric pig liver will be feasible. Milestones 1-4 appear to address the former; milestone 5 will demonstrate the functionality of the chimeric liver compared to controls in terms of human protein production. • The applicants have to show that within the proposed timeline, they can, in fact deliver a chimeric humanized pig liver that functions normally, lacks zoonoses and does not demonstrate hyperacute rejection. Additional concerns revolve around the lack of discussion regarding the endothelium of the chimeric liver. It is possible that the genetic modifications to overcome hyperacute rejection might address this potential issue. • While claims for eliminating chronic rejection are made these do not seem to be provided and because of the multiple causes of chronic rejection are not likely to eliminate it - they are a good start; data could be provided regarding staining of the pig liver and its destruction following infusion of human blood as a control with a projection regarding how much might be reduced in the modified pig liver. • Inflammatory panel seems extensive for rejection determination; consider tapering against known markers coupled with complement staining of the liver. • If porcine retroviruses are identified in effluent or in human liver construct, it would be helpful to know what next steps would be. • The goal of generating a humanized liver seem not to be achievable in the funding period.
No: 1	• The grant application is around the creation of a human liver in a pig. They do not show the ability to grow the fetal pig into a full term pig. • The project does not address the endothelium of the liver - does not address the potential for rejection. • Do not have critical preliminary data on ability to get pig into the surgical suite within 3 years. It would be great to see more documentation around meeting the 3 year deliverable.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 15	• The project outcomes would inform the development of a therapeutic product that would serve the unmet medical needs of the diverse population of California, including underserved racial and ethnic communities. The discussion on DEI directly addresses these issues in a satisfactory manner, with the understanding that the technology is relatively early in development. An additional source of livers will undoubtedly make transplantation a more timely, effective, and equitable treatment. • Addressing liver transplant for all has the potential to increase accessibility to the underserved. • Liver disease impacts people of all ages, races, and ethnicities. By attempting to generate a large supply of immunologically compatible liver for human transplantation, the project, if successful will improve access to liver transplantation for a broad range of people, including underrepresented minorities. • In this early stage of development, the project does not directly plan and design the studies to address and account for the influence of race, ethnicity, sex and gender diversity. That said, the overarching goal of the project is to create human livers in pigs for transplantation into diverse populations of all ages, ethnicities, gender, and race. Disparities amongst these groups could be, at least partially, ameliorated with an adequate supply of transplantable livers.
No: 0	*none*

Application #	DISC2-15137
Title (as written by the applicant)	Inhibitory interneurons derived from human induced pluripotent stem cells to treat stroke
Research Objective (as written by the applicant)	Allogeneic human induced pluripotent stem cells-derived inhibitory interneuron therapy product encapsulated in a hyaluronan/VEGF nanoparticle hydrogel for the treatment of stroke
Impact (as written by the applicant)	Previous stem cell-based technologies had poor survival, differentiation, and minimal migration within the peri-infarct brain region and were unable to restore neurological functions after stroke.
Major Proposed Activities (as written by the applicant)	• Determine CV-HA-HIPSC-3I efficacy after stroke • Characterize cellular mechanisms of repair • Assess neural network function • Qualification of cell therapy product • Determine Mechanism of Action
Statement of Benefit to California (as written by the applicant)	The research project proposed in this application will develop a therapy for a disease with no treatment, stroke, that is common and devastating in its consequences. Stroke affects thousands of Californians every year. The intellectual property for this therapy is held by [a California institution] and commercialization will directly benefit the State of California.
Funds Requested	$2,140,122
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	84
Median	85
Standard Deviation	4
Highest	90
Lowest	75
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	10
(1-84): Not recommended for funding	5

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 15	• Restoring function after stroke is a highly relevant clinical goal and the prevalence of the condition combined with unsatisfactory therapeutic approaches represent a considerable unmet medical need. • The proposed product represents a novel graft population that might have efficacy in a stroke model • There is an urgent need for improved treatment for stroke. The goal of this project is to test multiple eligible donor lines as a source of hIPSC- derived interneurons that will be encapsulated in a new hydrogel. • Cell therapy for stroke is an important topic. Please note the extensive literature on developing cell therapies using rodent models of stroke over the last 20 years. None of these approaches has translated into clinical applications even though functional recovery in behavioral tests is typically reported. This proposal may also experience the same outcome as previous attempts if key challenges are not addressed at this early stage. • The following are only a few examples from the literature using various approaches (cell grafting and recruitment of endogenous progenitors) to treat stroke but did not lead to successful clinical translation: PMID: 12161747; PMID: 12202033; PMID: 15959458; PMID: 12379868; PMID: 29909038; PMID: 19500468; PMID: 23296344; PMID: 19095993
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 15	• Interneurons have emerged as a potential useful cell transplant population for various injury models. The idea that these cells might also be beneficial in the stroke model is reasonable. • The applicant stated that interneuron transplantation into stroke have shown large cell survival and integration into the host with functional recovery, but no literature is cited to support this claim. • Preliminary non-clinical studies indicate that transplantation of the proposed product at either subacute or chronic stages post-stroke was associated with survival of the transplanted cells and their migration widely throughout the brain. The cells displayed repetitive action potentials, promoted axonal growth, reduced cortical loss, and enhanced recovery of motor function. • In previous work supported by CIRM, this group optimized the biopolymer hydrogel to support the interneurons through the initial transplant stress, and the best hydrogel developed in this several year effort is the one to be used in the proposed project. • They have recently developed the circuit mapping techniques and cell isolation approaches in this model that will be used in the proposed studies. • In Figure 6, they show that transplantation at 7 days or 30 days appears to enhance recovery. They also are using the rigorous approach of testing whether the cell line being used produces more complete behavioral recovery than any of the different biomaterials/stem cell progenitor populations possible. In the footfall assay used, their transplants produce notable improvement. • The general rationale is sound but underestimates the challenges. Reproducible derivation and in-depth characterization of iPSC-derived transplant material is essential and can/should be optimized by the investigators (e.g., RNA-seq). Once cells are grafted, the in vivo events are typically not under the control of the investigators. • Functional recovery in rodent models of stroke has been extensively reported previously. These findings may have various explanations and one needs to be cautious with extrapolating to the human brain. To firmly establish a scientific proof of concept, it would be necessary to establish a well-characterized strategy for iPSC differentiation and then develop a plausible rationale based on the anatomical organization/reorganization of the cortex and cell type-specific interneuron function. • Here are other open questions: 1. How would inhibitory interneurons known to be local-circuitry neurons innervating specific portions of pyramidal neurons, which are lost here due to stroke, regenerate and restore the function of the primary motor cortex? 2. How would migratory/undifferentiated interneurons in unrelated brain regions (including white matter tracts and contralateral hemisphere) affect a specific motor function, which serves as an assay endpoint (Fig. 6)?.

	• Literature cited by the authors does not describe the interneuron differentiation protocol outlined in this proposal. • Figure 7 shows green cells (perhaps GFP expressing?) including high level of background/unspecific staining but the authors describe that interneurons will be transfected with [a marker with red fluorescence]. Also, these experiments would require confocal analysis and the use of additional cell type-specific markers. • Fast repetitive action potentials are best studied for parvalbumin-positive interneurons (also called basket cells) innervating the perisomatic region of excitatory pyramidal neurons (PMID: 29621485; PMID: 37565421). One should not assume that this a general feature of all interneuron subpopulations, which have different anatomical, neurochemical, and electrophysiological properties (PMID: 25239808).
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 13	• The project is extremely well planned and appears to be meticulously designed. • The applicant provides compelling preliminary data showing that transplantation CV-HA iPSC interneurons show considerable functional recovery compared to all the other groups the applicant tested. Interestingly, cell transplants alone are not efficacious, which is an interesting result on its own and underscores the need for proper encapsulation. The analysis shown in Figure 6 is rigorous and convincing. • Cell migration and survival as shown in Figure 7 was good and suggests efficacy. • The cell product is poorly defined; more data as to the reproducibility of of the cell batch are necessary.
No: 2	• The generation and characterization of the transplant material is not convincing. It is unclear what is being transplanted and the authors did not provide convincing information on iPSC-derived interneurons. Immunostaining in Figure 4 is not convincing. Based on the published literature, CALB2 and SST are not co-expressed in the same interneuron subpopulation (PMID: 8915675). RNA-seq experiments should be performed, which would also clarify if other neuronal phenotypes are generated. • Details missing for iPSC cells and when to transplant. • Lack of details of the interneurons; not well characterized and not considered. • Nothing around scalability for the cell product.
GWG Votes	**Is the project feasible?**
Yes: 14	• The project is well constructed and has a logical organization of milestones and success criteria. Subacute and chronic injection paradigms are analyzed and the applicant proposes a comprehensive set of studies that would provide information as to the mechanisms that are associated with beneficial outcomes. • Very expert team with preclinical models and stroke. • This group has already developed and manufactured cell lines. • Milestones and outcomes are logical and likely to be achieved, and the preliminary data strongly support feasibility. • The applicant has shown feasibility of all the proposed approaches and preliminary data are strong. The impact of outcomes outcomes of a previously related CIRM funding should have been addressed. For example, have the preliminary data been generated under this previous funding? If not, are outcomes comparable? • Milestone 4 is underdeveloped. Sequence data shown in Figure 12 represent 5% of the total number of cells injected, raising concerns of whether and to what extend the transcription profile represents the cells that contribute to repair. • The project is feasible but highly risky and currently not set up for translational success. Much more work is needed to demonstrate the generation and convincing characterization of the transplant material. • A weakness is batch to batch variability. More rigorous work around the cell product needs to be done to establish markers and assays for reducing variability.
No: 1	*none*
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**

Yes: 15	• Both sexes are included in the study and cells are generated from a number of different cell lines. Overall the plan addresses and accounts for influence of sex and potentially ethnicity. • Stroke mortality rates are higher in Black Americans, American Indians, native Hawaiians, and other Pacific islanders, as compared with White Americans. • Poorer patients and families tend to have poorer post-stroke functional outcomes. • The PI has demonstrated a deep involvement in development of students from diverse communities. • The authors provided some ideas to address DEI.
No: 0	*none*

Application #	DISC2-14907
Title (as written by the applicant)	A First-in-Class Treatment for Progressive Multifocal Leukoencephalopathy Via Multimodal Immune System Engineering
Research Objective (as written by the applicant)	We propose to discover genome- and epigenome-edited allogeneic T cells engineered to selectively target JC virus (JCV) as a potentially lifesaving treatment for progressive multifocal leukoencephalopathy (PML).
Impact (as written by the applicant)	If successful, we would revolutionize treatment for PML patients in whom T cell immunity cannot be restored or boosted and unable to wait for adoptive transfer of donor-derived cell-based therapies.
Major Proposed Activities (as written by the applicant)	• In vitro evaluation of JC virus-specific T cell receptors (TCRs) • Multiplex engineering to develop an allogeneic T cell product • Epigenome editing of T cell product to enhance on-target potency • In vivo evaluation of engineered JC virus-specific TCRs • Identify additional JCV virus-specific TCRs for ethnically diverse HLA-A haplotypes • Isolate and evaluate high affinity TCRs to expand capacity of therapeutic opportunities
Statement of Benefit to California (as written by the applicant)	The proposed research will benefit the State of California and its citizens by developing a therapy accessible to patients of diverse backgrounds. While our focus is to develop an allogeneic T cell therapy for PML, once the bench-to-bedside therapeutic pipeline is built, it can be leveraged to develop therapeutics for other neuroinflammatory diseases with antigen-specific, CRISPR-engineered cell therapies, offering neurologic patients a potentially effective and curative therapy.
Funds Requested	$2,182,396
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	84
Median	85
Standard Deviation	5
Highest	93
Lowest	78
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 project hold the necessary significance and potential for impact?
Yes: 14	• This proposal is focused on developing a therapeutic candidate for progressive multifocal leukoencephalopathy (PML), which is a devastating central nervous system infection caused by JC virus. This virus causes a typically benign infection, but in chronically immune compromised patients, PML is almost universally fatal if the patient's immune system cannot be rapidly reconstituted. Even with immune reconstitution, 30 to 50% of patients die in the first few months and there is ongoing disability in 70% of survivors. • Because this product is designed in such a way that it would not have to be newly derived for every patient, success in this proposal could have revolutionary implications for the treatment of PML. • The first in class emphasis on multimodal engineering and non viral manufacturing of a cell product is exciting. • Producing an "off-the-shelf" allogeneic anti-JC virus combined HLA CD4+ and CD8+ T cell therapy (as proposed) would be the only timely option for individuals with PML. Building engineered cells from basic stem cells, while making them broadly immune-compatible, takes the best of many worlds. While there are many steps in this proposal, they're all designed from the beginning to address different aspects of later translation, so this proposal has potential for impact. • The proposal addresses unmet need in this deadly disease. • The proposal is in line with the CIRM mission.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• Yes. In particular, the concept of stripping off reactive epitopes and engineering JC sensitivity makes total sense for a rapid (near) universally applicable therapy. There is appropriate preliminary data for each aspect of the project but honestly there's a long way to go on each front as well, which is where the reputation and track record of these labs comes in. • Because this product is designed in such a way that it would not have to be newly derived for every patient, success in this proposal could have revolutionary implications for the treatment of PML and other viral diseases. • The proposed approach may overcome the problem that the first generation autologous and haploidentical donor-derived cellular therapies can take months to manufacture, during which time many PML patients suffer severe neurologic disability and death. • The project is particularly focused on identifying T cell therapies for HLA- A1, A3, A11, A84, and A30, which are the dominant HLAs in the United states. Some of these HLA types are more frequent in North American Natives, Hispanics and in Asian populations. • The work proposed for PML can be leveraged and used in other diseases. • The application utilizes highly sophisticated cell reprogramming. • Although the applicants indicate that they can identify virus-specific TCRs, they do not provide in vitro evidence of this.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 13	• The applicant team is comprised of a major lab handling each aspect of the project, and from the beginning this project is designed to be a therapeutic, with very little basic science work - just figuring out how to use existing genome engineering approached to achieve the product functionality. These are some of the world experts on their respective aspects of the project, and that shows in terms of thoughtful cutting edge approaches to achieving their milestones. • The project team includes members with expertise in every relevant facet of product development, from fundamental virology and neuroimmunology to targeted immune cell engineering to manufacture of therapeutic cell products and clinical expertise in treating patients with PML. • The proposals for progression and translation are well thought out, and are based on adaptations of existing T cell engineering approaches.

No: 1	• Some experimental details, such as effects of expression of endogenous TCR beta, are not addressed.
GWG Votes	**Is the project feasible?**
Yes: 13	• The applicants present very detailed (and logical) milestones which are aggressive but achievable by this group. While this is a thoughtful cutting edge project, there are multiple facets that all need to succeed for the project to advance, so that's the primary weakness, although it's frankly unavoidable and many backups have been proposed as well. The applicants are a powerful team with experience in TCR discovery, non-viral CRISPR engineering, T cell manufacturing, neurovirology, and clinical management of PML patients. • The milestones and expected project outcomes are very well thought out and logical, and appear likely to be completed within the scope of this application. • The project team has extensive experience in TCR discovery, non-viral CRISPR engineering, T cell manufacturing, neurology, and clinical management of PML patients. • The applicants have already identified a panel of candidate TCR's that target the JCV VP1 protein restricted to the HLA- H2 allele. This is seen most commonly in the North American population. VP1 is known to be involved in successful immunity against JCV, although knowledge of the specific epitopes in the protein targeted by T cells is limited. • The VP1 amino acid sequence thus far identified as primary interest is not a molecule with any human protein homolog, suggesting a low potential for inducing autoimmunity. • High avidity TCRs from the VP1 stimulated T cell population have been isolated, providing a robust pipeline for TCR discovery that will be expanded to additional HLA haplotypes. • The project employs a new nonviral CRISPR engineering platform that is currently in late stage preclinical development with a T cell receptor alpha chain locus for treatment of multiple myeloma. • It is a strength that immunogenic antigens were synthesized for validation.
No: 1	• It is not clear how allogeneic rejection will be tested. For the tumor model proposed in the final aim, the tumor cell line is not described.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 14	• The HLA types were selected to make the therapy broadly applicable. The individuals who have trouble with JCV likely already have other significant health issues which have led to them being immunocompromised, so this therapy is going towards a vulnerable, often minority, population. • People with poor access to regular healthcare, and people living with HIV who have poor control of the HIV infection, are disproportionately affected by PML. • Finding HLA matched donors for African, Asian, or Hispanic descent, or those who have genetic admixture, can take time and is inherently disadvantageous towards minorities of less represented HLA's. This proposal aims to address that disadvantage.
No: 0	*none*

Application #	DISC2-14899
Title (as written by the applicant)	RNA-based therapeutics to augment regulatory T cells: a novel approach to treat myocarditis
Research Objective (as written by the applicant)	Use human cell therapy insights, specifically CDC-secreted EV analysis, to develop a noncoding RNA chemical entity for myocarditis treatment.
Impact (as written by the applicant)	Key knowledge gap is how to recruit adaptive immunity to limit inflammation/heart injury in myocarditis. Boosting regulatory T cells is not yet a viable option.
Major Proposed Activities (as written by the applicant)	• Investigate the mechanism(s) by which BCYRN1 mediates proliferation of human regulatory T cells • Investigate the mechanism(s) by which BCYRN1 enhances migration of human regulatory T cells • Investigate the mechanism(s) by which BCYRN1 increases IL-10 in human regulatory T cells • Synthesis and evaluation of BDSS on human regulatory T Cell function: proliferation, migration, IL-10 production and suppression activity • Therapeutic candidate selection based on in vitro efficacy data • Assess in vivo the therapeutic potential of the chosen Therapeutic candidate in a CVB3-induced myocarditis mouse model
Statement of Benefit to California (as written by the applicant)	Myocarditis can affect people in California just like anywhere else. It can be caused by a viral or bacterial infection, and there are currently no effective treatments to limit damage to the heart. Developing RNA drugs for myocarditis that recruit regulatory T cells could potentially offer a new therapeutic approach to limit heart damage and improve outcomes for patients in California, thus improving the overall health and well-being of Californians.
Funds Requested	$2,264,509
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	2
Highest	85
Lowest	80
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	8
(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 project hold the necessary significance and potential for impact?
Yes: 15	• The applicant seeks to develop a candidate to augment Treg number and activity for the treatment of inflammation. They propose to investigate BCYRN1 or its synthetic BDSS derivatives as a novel RNA-based approach to treat acute myocarditis. If successful, the ability to modulate immune cells, such as Tregs could significantly improve patient care and address a critical roadblock to the development of therapies to control and modulate the immune system for a number of medical disorders. • The goal is a non coding RNA-based therapeutic to augment regulatory T cells: a novel approach to treat myocarditis. • The project would develop an RNA-based therapeutic that could treat myocarditis. There are few effective treatments for myocarditis so the project clearly addresses an unmet medical need. • The project may also have impact on other inflammation-related disease. • The progression from candidate evaluation in vitro to assessment in early stage preclinical rodent models of viral myocarditis is logical.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• At face value, the proposed project is based on sound scientific rationale, i.e., deliver increased numbers of Tregs to the inflamed heart by promoting cell proliferation and migration, and increase the production of IL-10 as an anti-inflammatory cytokine. There is currently no way to enhance Treg presence in the setting of acute inflammation. It remains to be seen as to whether enhanced presence and increased cytokine release are effective in the condition of acute myocarditis. • Preliminary data is presented in support of the feasibility for each of the 6 milestones. The first 3 investigate the mechanisms by which BCYRN1 mediates proliferation, migration and increased production of IL-10 by human Tregs; activity 4 focuses primarily on the synthesis and characterization of BDSS; activities 5 and 6 involve both in vitro and in vivo testing of the candidates. The data is compelling and well presented. It is provided in generous detail and almost entirely unpublished. • Excellent preliminary data. • Is one long non-coding RNA an answer? May need more preliminary data to support this.
No: 1	• The proposal contains preliminary data supporting the notion that BCYRN1 and derived RNAs regulate Tregs via IL-10 production. Data indicate anti-inflammatory effects in vitro. • Preliminary data using an in vitro autoimmune myocarditis model show a small effect. Other in vivo data are not directly related to myocarditis (e.g. MI data). The lack of compelling data using a relevant in vivo myocarditis model raises concerns about whether the in vitro immune modulation will lead to an effective therapeutic. • Concerns about the lack of compelling preliminary data to support the efficacy of the proposed candidate in vivo and of consideration of possible off-target effects.
GWG Votes	**Is the project well planned and designed?**
Yes: 14	• The project is appropriately planned and designed to achieve the expected outcomes, including proof-of-concept data for a product candidate that is ready to advance to translational studies. No allogeneic cell components are involved. The applicant has already generated strong preliminary data in support of success within the 36 month timeline. In addition, the product therapeutic could potentially be used for the treatment of a wide variety of inflammatory disorders. • This is a well-constructed, quality project with relatively low risk. The experimental design is logical and supported by strong preliminary data. Potential pitfalls and alternative approaches are considered; and the research plan would suggest that the project could be completed within the timeline of 36 months. Activities 1-3 investigate mechanisms of action; activities 4-6 investigate function, efficacy, and application to an in vivo CVB3-induced myocarditis mouse model.

	• Potential pitfalls are adequately discussed and alternative approaches presented for each of the six milestones. The team considered potential roadblocks and challenges for the studies that were designed. The overall strategy, methodology, and analyses are well-reasoned and appropriate to accomplish the activities/milestones of the project. Perhaps the greatest challenge is delivery and targeting to the Tregs. • The study is well-designed to identify therapeutic candidates and to determine if they are effective in early stage preclinical models. If successful, the candidates will be ready for more translational studies. • The project is very well-designed to evaluate the effects of the candidates on Tregs in vitro and to investigate selected candidates in a murine viral myocarditis model. • Experiments are clearly focused and detailed to address goals related to candidate identification, optimization, evaluation and mechanism of action. • Well designed, good controls and strong path to translation. • In vitro and in vivo studies are complementary. • Lack of targeting specificity is a concern. • Off-target effects are discussed as a possibility but not sufficiently assessed. • Preliminary data show very minimal effect in a different disease model that might not fully be comparable to acute myocarditis.
No: 1	• The autoimmune model is not the best option.
GWG Votes	**Is the project feasible?**
Yes: 15	• The proposed milestones and project outcome are logical and likely to be achieved within the proposed timeline of 36 months. This is based on strong preliminary data, expertise within the research team and the feasibility of targeting Tregs as a therapeutic modality for the treatment of myocarditis. The approach embodies a new paradigm for drug development that could possibly lead to a new gene therapy approach for the treatment of myocarditis and other inflammatory diseases. • The milestones are very well-designed. A lot of work is proposed, but the study is feasible within the proposed timeline. • Very clear and quantitative milestones for each of the aims are provided. • The PI of the project is a well-trained postdoctoral researcher and will direct and supervise all aspects of the research including the lab members of the team, who are TBD. Additional personnel include minimal effort senior faculty who will basically consult on experimental design, data analyses, and the like. Together, it appears that the investigators have complementary and integrated expertise for the proposed studies. Additional hirings will include a postdoc and research associate.
No: 0	*none*
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 11	• The project addresses sex and age in the experiment design - mouse myocarditis model. • Cardiovascular disease affects the entire population but poses a greater burden on underserved communities. If successful the therapeutic developed here would impact a diverse population. • The project plan and design of the research adequately address and account for the influence of race, ethnicity, sex and gender diversity. The applicant institution is committed to making the therapeutic available and accessible to all underserved racial/ethnic populations. The institution has developed a diversity and inclusion framework that includes key areas of focus that are particularly attuned to unmet medical needs. • The applicant institution has strong programs in DEI, although the relationship to this specific project is not clearly described. • Not well developed.
No: 4	• There is no effort to link to CA communities.

Application #	DISC2-14963
Title (as written by the applicant)	Development of an Optogenetic Vision Restoration Gene Therapy Using an Engineered Form of Melanopsin
Research Objective (as written by the applicant)	The objective of this research proposal is to develop a lead AAV candidate for an optogenetic vision restoration therapy for patients suffering from blindness due to loss of photoreceptors.
Impact (as written by the applicant)	Our optogenetic vision restoration AAV gene therapeutic candidate would non-invasively restore sight to patients terminally blinded by photoreceptors loss.
Major Proposed Activities (as written by the applicant)	• Complete Retinal Explant Characterization of Optogenetic Candidates and Select Leads • Complete Development of an Optogenetic Retinal AAV Expression Cassette (pOR) • Generate & Evaluate AAV Test Candidates for Animal Studies • Visual Rescue of Blind Rd1 Mice with AAV Test Candidates • Complete Tropism, Biodistribution, and Tolerability Evaluation of Lead AAV in large animals.
Statement of Benefit to California (as written by the applicant)	Blindness imposes both a personal burden on patients as well as a financial burden upon the State of California due to costs related to care and loss of productivity. With the number of blind people set to increase due to aging demographics and increased prevalence of blinding diseases such as dry age-related macular degeneration (AMD), a therapeutic to restore vision would provide relief to both Californian patients & their families personally and as well as the state through reduced care costs and increased productivity.
Funds Requested	$1,150,820
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	5
Highest	87
Lowest	75
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	8
(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 project hold the necessary significance and potential for impact?
Yes: 15	• Optogenetics is a promising approach to addressing vision loss, a major unmet medical need. Melanopsin is a strong candidate for an optogenetic tool as it taps into vision molecular signal amplification, is endogenously expressed in intrinsically photosensitive retinal ganglion cells (RGCs), and it can source its own chromophore. • The application provides a well-considered plan to develop new melanopsin mutants with greater light sensitivity and faster kinetics, potentially enabling restoration of vision at ambient light levels. • Overall, this is an exciting optogenetics approach with high potential to advance the field, to be undertaken by a group well positioned to launch future clinical trials. There is risk that the new melanopsin may not be rapid enough to improve functional vision, but the strengths of melanospin well justify its exploration. • Blinding diseases remain a significant unmet need. • This is an approach that can enable independence in activities of daily living and ability to navigate to legally blind individuals. • Previous clinical precedent has proven that this approach and type of product works. • The applicant organization is well positioned to translate this therapy into clinical trials. The PI is well-trained in the field. • The applicants have strong preliminary data, although a direct comparison to other opsins is needed, and controls are not presented in preliminary data. It is unclear how fast their candidate opsin is when compared to other opsins or how much relatively faster the kinetics of melanopsin can become. • The authors do not explain much about whether they think the improvements in opsin are sufficient to achieve meaningful vision restoration. Furthermore, the mouse experiments are very basic, and optometry and visial evoked potential testing may not fully characterize visual behavior or acuity. • The timeline for mouse studies is highly optimistic, and it is unclear that the applicants can afford the planned number of animals for their large animal study with the proposed budget.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 15	• Yes, there is a huge unmet need and this is an area of active research. This proposal will accelerate the likelihood of a genetic therapy that improves patient needs. The applicants already have identified lead protein candidates and have an AAV that is retinal specific and has been in humans and large animals. The applicants are actively derisking the development process as much as they can. • There is significant need for advances in this promising but nascent field, and the choice to start with melanopsin as a starting material is well justified. • The applicant has presented a very well thought out process and plan for developing a viable lead gene therapy lead candidate. • Engineering RGCs with these receptors is sound. • The opsin transgene and expression cassette will be delivered in vivo by a highly retinotropic capsid. • Intravitreal injections of the proprietary capsid are well justified.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 13	• The applicants have discussed potential pitfalls and addressed risk mitigation. • The project is well designed, although the applicants want to move quickly and rapidly advance to large animal studies, making the tight timelines perhaps unrealistic. • The project is well planned, although there may not be sufficient time allocated to complete the proposed mouse experiments.
No: 2	• The transduction of RGCs may not be efficient enough to produce a functional response. The preliminary data on this point is lacking.

	• Benchmarks against wild type or other state-of-the-art receptors are not provided in the preliminary data. • The large animal study may be underpowered given budget constraints.
GWG Votes	**Is the project feasible?**
Yes: 13	• The applicant is well positioned to complete the proposed study and to propel the therapy forward to the clinic. They have significant experience in retinal gene therapy, including with the capsid and with the difficulties involving immune response to this capsid that will be important for successful completion of this study. • Timelines are tight, and the amount of work is overzealous.
No: 2	• Large animal studies are proposed but feasibility within the time and budget is not clear. • The large animal studies are too ambitious and unlikely to be finished within the timeline and with the budget. • The animal experiments are too ambitious for the personnel budgeted.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 15	• The applicants have a strong relationship with the patient advocacy group Foundation Fighting Blindness. • Partnership with the Foundation Fighting Blindness is a strength of this proposal. The vague suggestion that the applicants will work toward reducing the costs of gene therapies to better serve populations in need is not explained, and would be difficult to achieve, although it is a worthy goal. • Although the intention to uphold principles of DEI is stated, the DEI strategy is unclear. Given the high costs of gene therapy, these therapies are out of reach for many. The applicants emphasize they are interested in lowering the price of gene therapies for patients, and increasing access for people with limited access to health care, which is a worthy goal, but do not state how this may be achieved.
No: 0	*none*

Application #	DISC2-14900
Title (as written by the applicant)	Developing a breast cancer stem cell drug
Research Objective (as written by the applicant)	To make a drug that kills breast cancer stem cells
Impact (as written by the applicant)	Metastatic breast cancer is incurable. The goal is to make a drug leading to cures.
Major Proposed Activities (as written by the applicant)	• Make a novel drug that potentially more effectively treats breast cancer with less toxicity. • Test the drug for efficacy and toxicity.
Statement of Benefit to California (as written by the applicant)	Breast cancer is the most common cancer in women. Once it has spread, breast cancer is not curable. If this project is successful, it will be the foundation for the advancement of a new, less toxic, potentially curative breast cancer drug to the women of California.
Funds Requested	$2,293,051
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 84

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

Mean	83
Median	84
Standard Deviation	4
Highest	90
Lowest	78
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	6*
(1-84): Not recommended for funding	8

* See Minority Report below

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 14	• Triple-negative breast cancer (TNBC) is the most aggressive form of breast cancer and new therapies are urgently needed. Selective targeting of TNBC stem cells has potential for a curative therapy. The proposed project addresses a major challenge in the current

	developmental therapeutics for TNBC and other types of cancer - the lack of selective targeting of cancer vs. normal stem cells.
	● There is unmet need in breast cancer and, more broadly, in metastatic disease.
	● TNBC represents a pressing medical challenge, demanding innovative treatment approaches to enhance patients' survival and well-being.
	● The envisioned therapeutic candidate involves a potent and selective small molecule from a class of compounds that have demonstrated promise in treating various solid and non-solid tumors.
	● The candidate will likely target TNBC stem cells by specifically targeting a CDK antigen (CDK19) that is expressed on the surface of breast cancer stem cells and not on healthy stem cells.
	● A recent published paper from the applicant's team identified CDK19 as critical for survival of TNBC stem cells, but not normal stem cells. Therefore, the proposed development of CDK19-specific and selective small molecular inhibitors would have a major impact on development of a safe and effective drug for patients with TNBC.
	● Currently, these CDK19-targeting small molecules are at least equivalent to CDK8/CDK19-targeting small molecules. Dual inhibition of CDK8 and CDK19 leads to multi-organ toxicity in in vivo studies. The selective antigen-targeting therapeutics are expected to exhibit a significant decrease in toxicity as compared to dual inhibitors as well as common chemotherapeutics.
	● This is promising. However, it would be valuable for the applicant to establish direct comparisons with analogous compounds.
	● If the proposed drug candidate effectively targets cancer stem cells it will represent progress in relieving a critical bottleneck in treatment of TNBC and other forms of cancer.
	● The applicant has already identified a promising lead compound and has an exceptionally well-developed strategy for the development and testing of more potent and selective leads. This proposal has a high likelihood of bringing a candidate to clinical testing.
	● The applicant has outlined a comprehensive plan for translation, encompassing rigorous in vitro evaluations utilizing cell cultures and organoid models. However, the plan for translation could be improved.
	  ● While organoids offer valuable insights into bioactive compounds, they are poor replicates for the intricate tumor-microenvironment and immune system interactions should be acknowledged. Therefore, enhancing the in vivo experimental component is imperative.
	  ● This enhancement should include efficacy assessments, encompassing tumor eradication and potential immune system augmentation mechanisms.

No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	● There is a convincing evidence that targeting CDK8 (which is expressed in normal stem cells) is a major source of toxicity. This provides justification for the proposed development of more selective inhibitors. ● Another rationale is based on a recent publication demonstrating that CDK19 is involved in suppression of CAR-T effector functionality. Therefore, the proposed therapy would have both direct and indirect antitumor activity by killing cancer stem cells and activating immune cells, respectively. ● The scientific basis for the project is robust. Elevated expression CDK19 has been linked to unfavorable survival outcomes in breast cancer patients. Recent findings also highlight that inhibition of CDK19 may bolster anti-tumor immune responses. ● The emergence of small-molecule dual CDK8/CDK19 inhibitors in clinical trials, specifically for breast cancer and acute myeloid leukemia, reinforces the rationale for identifying enhanced and safer compounds targeting CDK19. ● There is a solid scientific premise for the proposal stemming from findings reported in the applicant's recent paper. ● The preliminary data are convincing in that the identified lead compound specifically targets the desired CDK19 antigen, and not the more broadly expressed CDK8 antigen, and that CDK19 is responsible for driving tumorigenesis. ● CDK19 is a logical target for a small molecule inhibitor since its function is required for survival of TNBC stem cells, but not normal stem cells.

	• Yes, the scientific rationale is sound. Prior small molecule candidates targeting CDK19 and one other CDK antigen (CDK8) are currently in clinical studies. Specific targeting of CDK19 may create a path for development of a therapeutic with an improved safety profile. • The initial data provide considerable support for the use of a CDK19 inhibitor as a promising candidate against TNBC. Notably, the specificity and cytotoxicity aspects find substantial validation in organoid models. • Crystal structure data inform direction for developing new screens for selection of more potent and selective inhibitors. • The candidate is within CIRM's scope as it targets tumor stem cells. • Although the proposed project doesn't focus on human stem/progenitor cells as a therapeutic tool, it underscores a targeted approach against cancer stem cells. This unique perspective adds to the project's innovation and potential impact. • Augmenting the project's strength would involve a direct comparison between CDK19 inhibition and the leading approach of dual CDK8/CDK19 inhibition, examining efficacy and toxicity parameters side by side.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**

Yes:
13
	• The project is well-designed with logically built milestones. Results with an initial pilot compound provide a proof-of-concept for the proposed study. It's likely that at least one candidate CDK19 inhibitor will be selected for IND-enabling studies at the end of the project.
	• Yes, overall, the proposal is well planned and designed. However, the proposal must include a plan to evaluate treatment-related reduction in cancer stem cells, through phenotypic evaluation and/or transcriptomics.
	  ◦ Drug-treated cells should be evaluated in tumorigenesis assays (through implantation in mice) to evaluate the hypothesis that CDK19 inhibition eliminates cancer stem cells.
	  ◦ Residual cells after drug treatment should be evaluated by flow cytometry or scRNAseq to verify stem cell targeting.
	• The project excels in generating and initially characterizing an inhibitor compound, establishing a solid foundation. However, the project's overall structure requires enhancement, particularly concerning the comprehensive evaluation of in vivo efficacy necessary for effective translation. To better align with DISC2's translation goals, the project's in vivo component requires further development.
	  ◦ Strengthening this facet involves designing efficacy studies that directly compare the candidate against the dual CDK8/CDK19 inhibitors in clinical trials. This comparative analysis should encompass tumor eradication efficacy and offer mechanistic insights.
	  ◦ Additionally, exploring the intricate interplay between the immune system, tumor microenvironment, and treatment response is crucial. Addressing vital factors such as administration route, dosage, and potential toxicities will contribute to a more comprehensive plan.
	• In terms of establishing a comparison between a selective CDK19 inhibitor and less selective CDK8/CDK19 inhibitors, I was satisfied by the preliminary data that the lead compound showed specificity for CDK19 over CDK8.
	• CDK19 vs. CDK8/CDK19 inhibitor studies are not necessary for achieving the goals of this project. The main purpose of the proposed study is to further develop a selective CDK19 inhibitor with minimal affinity for CDK8, the source of an unacceptable toxicity of the non-selective CDK8/19 inhibitors. The applicant already has a lead compound with some selectivity toward CDK19 versus CDK8 and will compare new, more selective CDK19 inhibitors with this lead. That's the appropriate comparison.
	• Pitfalls and alternative approaches: While technical challenges regarding compound selectivity are acknowledged, more emphasis should be placed on addressing potential efficacy-related hurdles and proposing alternative strategies to mitigate these challenges.
	• Excellent description of potential pitfalls and alternative approaches.
	• The project plan and timeline demonstrate an urgency that is commensurate with CIRM's mission.

	• The project timeline appropriately reflects the urgency aligned with CIRM's mission.
No: 1	*none*
GWG Votes	**Does the project uphold the principles of diversity, equity, and inclusion (DEI)?**
Yes: 14	• The project demonstrates a proactive approach towards addressing diversity concerns. Notably, patient-derived xenograft (PDX) tumors are sourced from a broad spectrum of ethnic backgrounds, encompassing African American, Hispanic, Asian, and Caucasian populations. Furthermore, the applicants emphasize their commitment to inclusivity by ensuring that any supplementary samples obtained during the study originate from members of underserved communities. • The project holds the potential to make significant contributions to addressing the unmet medical needs of California's diverse population. The clinically diverse nature of TNBC, including genetic risk factors like African ancestry, is recognized. • Notably, the application's data highlight the disproportionately higher incidence and mortality rates among women of African American and American Indian/Alaska descent during the 2015-2019 period. • The project plan and design adequately address and account for the influence of race, ethnicity, sex, and gender diversity. • The project outcomes inform the development of a new drug for patients with breast cancer that serves the unmet medical needs of the diverse California population, including underserved racial/ethnic communities. • Outstanding.
No: 0	*none*

MINORITY REPORT

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

This application was scored by 14 GWG reviewers. Scores ranged evenly from 78 to 90.
Reviewers broadly agreed that the proposal addresses an unmet need in breast cancer, that the rationale is sound and justified with preliminary data, and that the team, timeline, and resources are in place to support success of the project. Several panelists indicated the project was within CIRM's scope as the small molecule candidate to be selected will target cancer stem cells. The feedback on the applicant's DEI plans was uniformly positive.
The supportive minority (6 of 14) were impressed by the preliminary data and the applicant's project plans for candidate selection ("an exceptionally well-developed strategy"). Regarding the preliminary data, they emphasized the applicant's success to date in identifying a lead, or 'pilot,' compound with appropriate characteristics, evidence that specifically targeting CDK19 has potential for therapeutic potency via two pathways (killing cancer stem cells directly, and activating immune cells to attack the cancer), and evidence that targeting CDK19's paralog CDK8 is a major source of toxicity of dual CDK8/CDK19 inhibitors currently in clinical testing. One supportive reviewer had constructive feedback on the project plan for the applicant and CIRM staff to consider in advance of project launch, but in overview found the proposal meritorious of CIRM funding in its current form.
The votes of the majority (8 of 14) reflect perceived limitations in the preliminary data and project plan. Two reviewers recommended studies for a more comprehensive investigation of efficacy, toxicity, and other parameters, to increase likelihood of meeting the DISC2 expected outcome - a candidate that is ready for translational stage activities by the end of the award. In overview, these reviewers hope the applicant will do a few more preliminary experiments and extent the project plan as recommended, and resubmit in the next DISC2 round.

Application #	DISC2-15114
Title (as written by the applicant)	Development of a VAV2 antisense oligonucleotide (ASO) treatment for ALS
Research Objective (as written by the applicant)	Utilize patient specific stem cells (iPSCs) to model ALS and identify a broadly acting therapeutic intervention
Impact (as written by the applicant)	ALS is a heterogenous patient population, and there is a dire need for broadly acting therapeutic interventions
Major Proposed Activities (as written by the applicant)	• Compare the in vitro efficacy of up to 10 lead candidate VAV2 ASOs to rescue the survival of iPSC-derived neurons from 30 locally and nationally recruited ALS patients • Determine the off-target gene expression effects of the 10 lead candidate ASOs • Select and evaluate the PK, PD, and safety of the lead VAV2 ASOs in vivo • Quantify VAV2 suppression and pharmacokinetics for the lead candidate ASOs in hVAV2-BAC mice • Assess glial activation and safety of the lead VAV2 ASOs in vivo • Assess safety and tolerability of lead VAV2 ASOs in rats (Months 18-24)
Statement of Benefit to California (as written by the applicant)	California has one of the largest ALS patient populations in the nation. Successful completion will not only identify a highly promising therapeutic for a broad spectrum of ALS patients, but will utilize the immense diversity within the state to more accurately probe the nuances of disease pathogenesis and assess efficacy in a highly unique patient population.
Funds Requested	$2,296,376
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 84

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

Mean	81
Median	84
Standard Deviation	8
Highest	90
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	7*
(1-84): Not recommended for funding	8

* See Minority Report below

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 15	• The application aims to develp treatment for amyotrophic lateral sclerosis (ALS). Today, there are no cures and extremely limited treatment options. • The research addresses ALS, a devastating neurodegenerative disease with limited therapeutic options, targeting an area of utmost clinical significance. • The applicants expect the ASO strategy targeting VAV2 to be effective for all familial forms of ALS and >75% of sporadic ALS patients, which would have significant impact. • The team not only identified a potential therapeutic target but also validated it with multiple antisense oligonucleotides, enhancing the reliability of the results. • The utilization of an unbiased genome-wide CRISPR-interference screen demonstrates a cutting-edge approach to therapeutic target identification. Their in vitro results were further corroborated with in vivo outcomes. • By targeting the pathology seen in over 95% of ALS patients, regardless of genotype, the study could benefit a broad range of ALS patients. • There is no cure for ALS and limited treatment options. • Yes, as there are no successful ALS therapies, and ASO approaches are in clinical trials. • The applicant presents plans for clinical translation and have also already initiated contacts with biotechnology company for further clinical and commercial development.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• The application has a clear goal to develop ASOs that suppresses VAV2, a guanine nucleotide exchange factor, for the treatment of amyotrophic lateral sclerosis. This approach is backed by previous studies. • The applicants have already screened >100 ASOs for their ability to suppress VAV2 in human cells. The focus of this project is to test their efficacy in preventing the degeneration of neurons derived from a large, diverse set of ALS patient iPSCs. Studies of effectiveness in a mouse model in vivo will also be performed and safety, tolerability, and pharmacokinetics will be assessed in rats. • The use of a 3D-spheroid culture system, while innovative, raises questions about how closely these systems mimic the in vivo environment and potential translational limitations. • The team's decision to focus on VAV2 is grounded in empirical data, as they identified its suppression to improve neuronal survival during their CRISPRi screen. This provides a solid rationale for further exploration of VAV2 as a therapeutic target linked to a ubiquitous pathological signature in ALS. • Using patient-derived cells provides a more accurate representation of disease pathology and enhances the rationale behind the therapeutic strategy. • The fact that VAV2 ASO-mediated suppression demonstrated functional benefits in a murine model of ALS, including extended survival, provides a compelling rationale for their proposed therapeutic strategy. • Demonstration that VAV2 ASO treatment ameliorates motor deficits and improves survival in a hTDP43 mouse model solidifies the promise of their approach. • While VAV2 suppression showed promising results, the application could have been strengthened by comparing its efficacy to other potential targets identified in the screen. • Yes, the proposal makes use of iPSCS and induced neurons from a large number of ALS patients to capture sporadic as well as several different familial forms of ALS. • The applicants present good arguments for a meaningful approach, supported by preliminary data. • The applicants have several candidates already.
No: 1	• The rationale is sound, but the likelihood of success is low, and even if it is achieved, there are major problems delivering the therapy that would result. • The level of preliminary data are less than what are expected or needed to support VAV2 as a target. Many of the references cited have evidence for at least several genes, so the particular evidence for VAV2 is non-unique. There is a lack of computational or network analysis done which would focus attention on VAV2. • Suppression of VAV2 does show positive data in the applicant's neuronal survival assay, although data are also presented for other genes which show better survival. In addition, it is not clear to what extent the neuronal survival assay, and associated biological

	implications, is the inverse of ALS pathology. Additional testing in C9orf72 lines would provide stronger evidence for pursuing VAV2. • It is an open question if the effects of VAV2 suppression on neuronal survival will result in phenotypic rescue. So while there is no doubt that VAV2 is a very interesting gene, the level of evidence provided in this application is more appropriate to support further exploration of the function of VAV2 rather than progressing to therapeutic development.
GWG Votes	**Is the project well planned and designed?**
Yes: 14	• The project takes a logical and step wise approach using cell and animal models already established in the applicant's lab. • The specific aims are constructed in a logical progression, starting from initial in vitro testing, moving to in vivo studies, and finally examining potential toxicity in rats, which emphasizes the translational aspect of the proposal. • The project holds high quality in ASO development, cell models used, and the extensive amount of patient material tested in this proposal. • Pitfalls and alternative approaches are adequately identified and addressed. • The applicant proposed a straight forward approach with a clear product profile. • The application is well written, including Aim 3, which focuses on pharmacokinetic and toxicity studies indicating that they are committed to progressing a clinical candidate. • The choice to test on induced neurons derived from a diverse panel of ALS patients from different geographical regions ensures the results' broader applicability and robustness. • Additional considerations on long-term effects or potential resistance mechanisms could further strengthen the proposal. • Administration of the ASO is anticipated to be problematic. The proposed characterization of kinetics, potential off-target effects and disease-relevant phenotypes in mouse models all are logical. However it is uncertain if at this point the preliminary data justify this level of investment at this stage, on this single gene. The application does not attempt to address well-recognized ASO brain delivery challenges.
No: 1	• The dose and delivery efficiencies need to be better explored in the proposal's design.
GWG Votes	**Is the project feasible?**
Yes: 14	• It is an extensive project plan but the proposal is feasible given the background and expertise of the team, plus the current availability of candidate ASOs and validated cell systems. • The team is well composed. • Feasibility is high, given that the candidate has already been identified. • The approaches the applicants will take are familiar, including the use of rat preclinical models. • The applicant has collaborations with a biotech company to support and help with clinical CMC scale up.
No: 1	• The delivery of the ASO candidate is not adequately addressed.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 15	• The applicants have generated iPSCs from a number of Southern Californian ALS patients that approximate the ethnic diversity of the Southern California ALS population, including multiple Hispanic patients and both males and females. • The applicants point out that ALS affects all genders/ethnicities. • The applicants participate in Community Listening Sessions within local communities of patients, caretakers, and their families. • The applicants have gathered additional lines from diverse populations to test the effects of VAV2 suppression.
No: 0	*none*

MINORITY REPORT

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

This application was scored by all 15 GWG panelists. Four panelists scored the application 70, four panelists scored between 79-84, and seven panelists scored between 85-90. Panelists generally agreed that the proposal addresses a critical unmet need in ALS and that the strong applicant team has taken a well-justified approach to the nomination of VAV2 as the therapeutic target. However, the votes of the majority of the 15 panelists indicate that further characterization of the function of VAV2, in particular whether the effects of VAV2 inhibition will translate to a phenotypic outcome and therapeutic benefit, should be further explored prior to this investment. The majority of reviewers also raised concerns about documented challenges of ASO therapeutic delivery for ALS and other brain conditions, and felt that these challenges were not adequately addressed in this proposal. Reviewers who recommended this application in the minority also noted some experiments that could further solidify support for VAV2 as the therapeutic target, but felt that the body of preliminary data supported progression of the ASO candidates that the applicants already have in hand. These reviewers also highlighted that the availability of candidate ASOs at this stage is a strong indicator of feasibility, and commended the applicants for their translational strategy and inclusion of experiments to derisk safety at this stage.

Application #	DISC2-14910
Title (as written by the applicant)	Human induced pluripotent stem cell-derived glial enriched progenitors for the treatment of mild traumatic brain injury
Research Objective (as written by the applicant)	Allogeneic human induced pluripotent stem cell-derived glial enriched progenitor (hiPSC-GEP) cell therapy to treat mild traumatic brain injury (TBI)
Impact (as written by the applicant)	Prior to this study, glial cell-based therapies have never been tested as a therapeutic candidate for the treatment of mild traumatic brain injury.
Major Proposed Activities (as written by the applicant)	• Milestone 1- Determine hiPSC-GEPs efficacy • Milestone 2- Characterize hiPSC-GEPs-induced mechanism of repair • Milestone 3- Determine plasticity and neural network connectivity changes
Statement of Benefit to California (as written by the applicant)	Mild traumatic brain injury is a devastating disease with no treatment. It is estimated that 100 to 300 per 100,000 people seek medical attention for mTBI annually worldwide. Nearly 32,900 people diagnosed with a non-fatal TBI are hospitalized in California each year. There is a crucial need for better therapeutic treatments towards enhancing recovery and rehabilitative mechanisms after mTBI.
Funds Requested	$1,931,806
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 83

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

Mean	83
Median	83
Standard Deviation	1
Highest	85
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 project hold the necessary significance and potential for impact?
Yes: 14	• Mild recurrent TBI is associated with high cost of care and no therapeutic approach is yet available. There is a great unmet need.

	• The applicant proposes to develop a cell therapy using a relatively newly discovered pro-astrocyte biased cell product where iPSC cells are exposed to a chemical to induce astrocytic bias. This is an interesting potential product. • This project will investigate the application of allogeneic human induced pluripotent stem cell-glial enriched progenitor (hiPSC-GEPs) in mild TBI. They generate GEP by exposure of iPSC-NSCs to a compound that alters the fate commitment towards immature astrocytes. They will examine four donor lines, and their cell therapy criteria is set to target specific populations with regards to age, sex/gender and post-concussion symptoms. • The proposed cell therapy candidate is interesting with the idea to produce pro-repair astrocytes for cellular therapy to improve the microenvironment of TBI for endogenous repair and regeneration. The applicants have set specific outcome measures to assess efficacy. They argue that this strategy has several advantages compared to existing methods including efficacy and permanent fate specification towards pro-repair astrocytes. • The applicant provides compelling data that show the ability to generate a relevant model with vascular damage, demyelination, and astrogliosis. The feasibility of the endpoints are also highlighted by behavioral assays the applicant has published before. • Proof of concept of the efficacy of the proposed cell population is demonstrated in a model of white matter stroke, but no preliminary data are provided using the mild TBI model. Thus the rational for a positive impact of the cells is purely based on the assumption that the white matter stroke model mirrors the mild TBI model. • The applicants have provided a translational road map. They will test four different stem cells lines and two therapeutic time windows (acute and chronic) for transplantation. Moreover, they have qualified the manufacturing process for hiPSC-GEPs through five criteria: safety, identity, purity, activity, and stability. • To demonstrate the scale-up manufacturing capabilities of the potential therapeutic product, the applicants will develop a new semi-close manufacturing protocol for phases 1 and 2 of a future clinical trial. This preliminary work could fast-track the Pre-IND and FDA approval for a future clinical trial for mTBI patients. • Yes, but at this early stage the applicants are still understanding mechanism of action. All the milestone are focused on developing and demonstrating efficacy both structurally and functionally. The applicants have not discussed CMC GMP issues, but they do have cells lines with assays and CMC quality assurance development considerations. There are no studies for safety or dose ranging considerations so these will still need to be done. • The applicants have only focused on mechanism of action for structural and behavioral / functional efficacy. There are no studies in this proposal for safety and dose selection. They also failed to discuss the next set of safety and dose ranging studies in larger animals. They did not mention the device development aspect as well as the surgical aspects (safety) of delivering these cells. There was also no mention of storage and transport of the cells. These are concerns for later in the development process, but nevertheless a consideration for even now.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• The rationale that young or immature astrocytes would have a beneficial effect when transplanted into injury models is not new and has been shown to have some validity in models of spinal cord and stroke by the applicants. • The new protocol of biasing cells towards an astrocyte lineage shows transcriptional profiles that are consistent with "beneficial" astrocytes but the mechanism that is behind this conversion is not clear. • The impact of transplanting these cells into an injury site on endogenous cells is not known, and the interaction with inflammation is not clear. Despite this, the cell population seems to have some advantageous properties and testing them in a model of mTBI seems reasonable. • Yes, the rationale is very sound. These PIs have extensive experience in this area with significant NIH/CIRM funding already. They have submitted a very complimentary grant to the DOD where TBI is a huge unmet need among military. However, it is unclear that the prelim evidence in the white matter stroke model translates to efficacy in TBI.

	• The applicant provides compelling rationale about the suitability of GEP transplantation and the benefits of transplanted immature astrocytes in repairing the injured brain and improving function. The rationale is supported by exciting proof-of concept data in which the applicants have studied and optimized identity, purity, and viability of these cells. • The project is detailed and built on applicants' models and experience supporting the proposed approaches. The use of human iPSC-fibroblast to generate NSCs and then GEP is the center point of this application.
No: 2	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 11	• The applicants will use an interesting model of repeated TBI that they have developed. This mouse model is designed to mimic TBI in athletes or military personnel who are prone to repeated concussion. hiPSC-GEPs have been successfully tested by the applicants for white matter stroke and vascular dementia with positive outcomes. The models show common pathology as mTBI. • This proposal has three major milestones to assess efficacy measured by behavioral improvement, with cognition being a major focus, to study repair processes as underlying mechanisms of potential improvement and to determine functional integration of transplanted cells within the neural network in TBI. • The project is structured logically and all the proposed approaches represent essential steps in identifying the efficacy and mechanisms of the proposed cellular therapy. Addition of ex-vivo electrophysiology for functional integrity assessment and snRNAseq of the brain cells to determine their response to engrafted cells are some strengths of the project. • Overall, the project uses cutting edge models and approaches that would increase the likelihood of identifying a cell-based approach for mTBI by introducing pro-regenerative astrocytes to the injury environment. • One weaknesses of the project is that it contains exclusive use of immunocompromised mice instead of testing the same strategy in immune competent mice. There is a high possibility that transplanted astrocytes may die in immune competent mice (a model more similar to human cases in reality). • The applicant has thus far only generated these cells from one iPSC line and it is thus not clear whether additional lines would show the same astrocytic bias. Thus approaches in milestone 1A that will analyze the end product from different founder lines are reasonable. • The applicant did not provide any preliminary data that would show efficacy of the cells in mTBI. The outcome of milestone one will be instrumental for other milestones of this application. • The applicant equates the outcome in the white matter stroke to the potential outcome in mild TBI, which might not be true. It thus might not be necessary to have an optimized solid product from various founder lines to show general efficacy in the mTBI model. • For mitigation strategies in Milestone 1A, if the expected improvement is not detected (despite what the applicants anticipate), the applicants mention that they will continue optimizing one of the lines. But there was no description on what improvement will be done. • In a revised application the applicants should demonstrate early preclinical evidence in more appropriate models of TBI. • The applicants did not rationalize why iPSC-fibroblast will be a control for the therapeutic instead of iPSC-NPCs, which are the competing cell type.
No: 3	• The exclusive use of immunocompromised animals is a weakness of this application. • Fibroblasts may not be the appropriate control cells in this context.
GWG Votes	**Is the project feasible?**
Yes: 14	• This application is from a skilled team with a good vision for translation. • The applicants have all the necessary resources to complete the project. • Given that all the platforms, the model, and experimental approaches are set and optimized, the proposed milestones and deliverables are realistic. The PI is a well-funded, established researcher with extensive expertise in TBI and neurodegenerative disorders.

	The co-applicant brings expertise in iPSC. In addition to the two PIs, there are three personnel involved. This provides adequate critical mass to undertake this research. • Yes, the applicants have mouse models that will demonstrate functional cognitive damage as well as histopathological changes that can be reversed with the hiPSC-GEP cell lines, although there are no studies around safety and or dose selection. This ia a well-constructed, quality project. • The applicants identify pitfalls for the studies but do no identify pitfalls from a drug development perspective. For example, they do not mention safety concerns such as tumorigenesis, the device development and/or surgical delivery safety related events, dose selection, or cell manufacturing, shipment, and storage. But these can be addressed in a Translational award. • Preliminary data showing survival and morphological readout in TBI would increase feasibility. • The feasibility of the application could be strengthened if they had shown the survival of astrocytes in mTBI model and not solely built on the previous findings in the white matter stroke model. • The applicant needs to generate some data using a TBI model system, and not a stroke model to support feasibility. • The rational for using six different behavioral tests after acute injury in the chronic injury model in milestone one is not clear and is not explained. • It is not clear under what circumstances milestone 2 and 3 will be initiated and why the specific time points are selected. It seems that these entire aims depend on the outcome of aim one, for which there are no preliminary data. • Milestone three seems highly premature considering that no data are shown to support that the cell graft would show any functional recovery on any level. • The preliminary data refer to vascular damage analysis. Such analysis is, however, not done in the proposed study, which calls into question the relevance of these preliminary data.
No: 0	*none*
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 14	• One strength of this preclinical project is its plan to investigate the outcomes of the proposed strategy in various age group representing juvenile, adult and aged animals as well as both male and female as sex affects the outcomes of TBI. • TBI has a high prevalence in the US and California. As such this research can potentially design a new approach for TBI repair. • Both investigators are involved in community outreach that will inform their research. They have been also active in promoting research at the undergraduate level to encourage participation of students from diverse backgrounds in research programs. The proposal describes disparity in TBI and how sex/gender and age influence the outcomes of TBI and will consider this in their preclinical design. • The applicant states that trials will have deliberate recruitment programs for underrepresented minorities, including outreach to diverse ethnic groups and programs to encourage gender diversity in the enrolled patients. However, in the current application, there is no mention of using IPC cells from different racial ethnicities or any comments on how the proposed product would benefit underserved groups. • DEI information is limited.
No: 0	*none*

Application #	DISC2-15030
Title (as written by the applicant)	Chemically engineered photoreceptors for vision restoration in retinal degeneration-associated blindness.
Research Objective (as written by the applicant)	This proposal will develop a cell-based therapy that can restore vision in retinal degeneration-associated blindness such as Stargardt disease and age-related macular degeneration.
Impact (as written by the applicant)	Chemically induced method will overcome inefficient differentiation techniques, potential insertional mutagenesis and time intensive quality assessment associated with pluripotent stem cells.
Major Proposed Activities (as written by the applicant)	• Human skin fibroblasts will be chemically induced to candidate photoreceptor cells. Chemically induced cells will be isolated and assessed for gene expression signature by single cell RNA sequencing. • Skin fibroblasts derived isolated chemically induced photoreceptor cells will be assessed for chromatin signature by single cell chromatin sequencing methods. • Function of chemically induced photoreceptor cells will be assessed by microscopic evaluation of calcium influx/efflux upon light stimulation and chemical treatments. • Isolated chemically induced photoreceptor cells will be injected into the retina of the rodent eyes to examine their potential for integration and survival inside the retina. • Chemically induced photoreceptors will be injected into the eyes of blind mice and rats followed by assessment of vision restoration by retinal electrophysiological & visual behavior tests. • Toxicity and mechanism of vision restoration after chemically induced photoreceptor injection will be assessed by microscopic analysis of transplanted retinal tissues.
Statement of Benefit to California (as written by the applicant)	Photoreceptor loss-induced retinal degeneration affects diverse racial and ethnic groups in California and all over the world. The proposed research will generate candidate photoreceptor cells from donor fibroblasts from diverse racial/ethnic groups. Successful generation of photoreceptor cells followed by vision restoration in preclinical animal models would pave the way for the application of this approach in a diverse population including the citizens of California.
Funds Requested	$1,873,700
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 83
Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	82
Median	83
Standard Deviation	2
Highest	84
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 project hold the necessary significance and potential for impact?
Yes: 14	• The project aims to restore vision in retinal degeneration, which is much needed. The product proposed could provide a therapeutic approach. • The expected outcome is a fibroblast-derived chemically engineered photoreceptor to restore vision in retinal degeneration-associated blindness. The cell product is based on chemical reprogramming of fibroblasts, rather than iPSCs. If successfully developed, this approach could accelerate clinical applications. • The applicant plans to manufacture chemically induced photoreceptors to be inserted into the eyes of mouse and rat models of blindness. • The project represents a generally applicable approach to treating retinal blindness. • New cell therapies for these diseases would meet an unmet need. • The applicant has presented options for progression but more details about translation would have been appreciated.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• The application includes a sound rationale for the choice of clinical problem, the biological mechanism and the use of direct conversion of fibroblasts. • The rationale is based on published research by the applicant team. • Chemical reprogramming could produce new cell therapies. • Such an approach could work. However, in the competitive context of photoreceptor production from other sources such as iPSCs and retinal organoids, it may not prove to be the best. • The applicant proposes in vitro calcium channel studies, activations, and then in vivo studies. Could they use a single in vivo model? • The dose response is not clear, and increasing dose is not necessarily better.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 12	• The project is well planned and designed. This is a clear and logical stepwise design. There is some lack of clarity in GMP reprogramming and how this will be achieved. • The structural and functional endpoints planned for the mouse studies are reasonable. The in vivo model studies include safety/toxicity assessments. • The project is very linear - later milestones are based on earlier milestones. • What is the purification of the cells, and why only 80%? What happens to the other cells in the eye, from a safety perspective?
No: 2	• There is good proof of concept data and the in vivo work requested in the last review has been done. Overall though, I still think too much is planned for a three year project. Manufacturing and biochemical, histological and behavioral studies - all repeated for five cell lines and also repeated in two rodent models, seems a lot and was a critique raised in their last submission. • The animal work should be more focused and designed precisely to evaluate dose. • Why manufacture rods and cones? Mice are rod-dependent, so why not just use rods?
GWG Votes	**Is the project feasible?**
Yes: 11	• The proposed milestones and expected project outcome logical and likely to be achieved within the proposed timeline. • The proposed team is appropriately qualified and staffed. • The team has access to all the necessary resources to conduct the proposed activities. • The budget is appropriate for the research proposed.

No: 3	• Preclinical data are lacking as to whether fibroblasts represent a potential advantage. • The work is still unlikely to be finished within the grant period. • The project appears understaffed and under-funded. • The quality of the cells produced is unclear.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 14	• The human fibroblasts will be from various racial/ethnic groups including White, African/American, and Mexican donors. The applicants also have plans to include fibroblasts from additional racial/ethnic groups. • The proposal includes good plans to ensure DEI principles are in place. There is a stated commitment to DEI and a commitment to diversity in selecting donors for fibroblasts. • The proposal contains plans for engagement with the patient community. • No concerns.
No: 0	*none*

Application #	DISC2-14943
Title (as written by the applicant)	Conversion of Glioblastoma into Induced Dendritic Cells as a Novel Immunotherapy using Custom-designed HSV Vectors
Research Objective (as written by the applicant)	Using herpes simplex virus vector to deliver cell fate genes, we will convert glioblastoma (GBM) into dendritic cells (DC) that are capable of stimulating T cells and GBM's inactive tumor environment.
Impact (as written by the applicant)	GBM is the deadliest brain cancer in adults with limited treatments. If successful, these studies will create a low cost, off-the-shelf gene therapy that forces GBM to initiate its own immunotherapy.
Major Proposed Activities (as written by the applicant)	• Determine conversion efficiency in GBM/GBM stem cells (GSC) using cell fate determinant genes (CFD) delivered by a non-oncolytic HSV (noHSV) vector and confirm DC functions of the created iDC-APCs. • Determine the mechanism of the GBM to iDC-APC conversion with the noHSV-CFDs using markers and genomic sequencing to track as tumor cells undergo conversion. • Determine clinical efficacy of iDC-APCs created inside the GBM tumor microenvironment by injecting the noHSV-CFDs directly into the GBM tumors. • Determine conversion efficiency in GBM/GSCs using CFDs delivered by an oncolytic HSV (oHSV) vector that causes some GBM cells to rupture and confirm DC functions of the created iDC-APCs. • Determine clinical efficacy of iDC-APCs created inside the GBM tumor microenvironment by injecting the oHSV-CFDs directly into the GBM tumors. • Determine whether the cooperation between iDC-APCs created in the GBM tumor and the oncolytic activities of oHSV inside the GBM tumor will enhance tumor growth control and survival.
Statement of Benefit to California (as written by the applicant)	Prognosis for brain cancer across racial and socioeconomic groups remains dismal with a 5-year survival rate of 7%. Current standard treatments are grossly inadequate. Existing immunotherapy has limited efficacy in brain cancer. If successful, these studies will create a novel gene therapy leveraging the patient's tumor cells to initiate their own anti-tumor immunity from within the tumor, which will benefit patients across racial and socioeconomic groups in California, the US, and the world.
Funds Requested	$2,240,642
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: 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	81
Median	81
Standard Deviation	5
Highest	90
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	4
(1-84): Not recommended for funding	11

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 13	• The applicants propose to develop and investigate an off-the-shelf fate conversion-based immune gene therapy for GBM using oHSV vectors. Specifically, the PI proposes to develop combinations of cell fate genetic determinants (CFD) to convert glioblastoma (GBM) stem cells (GSC) and tumors into induced antigen presenting cells with dendritic cell functions (iDC-APC). This will reheat the "cold" tumor microenvironment (TME) of GBM in order to reactivate anti-GBM immunity. • The goal of this project is to develop a novel immunotherapy for GBM, the most common and largely incurable brain tumor. • This is an innovative and significant discovery project. • GBM is a very high unmet need. • The proposed technology of in situ tumor cell reprogramming and converting them into effective APCs for induction of tumor-specific immunity could have a broad application for other types of cancer. • The proposed therapeutic candidate is likely to address the unmet need of GBM patients, especially elderly patients based on its convincing preliminary data. However most of the preliminary data has been obtained using tumor cells transduced in vitro. • Additional preliminary data obtained from either non-oncolytic or replication competent oHSV bearing CFDs in vivo will significantly enhance the feasibility of this project. • Similar approaches to the one included in this proposal have not progressed clinically.
No: 1	• Concerns about translatability of this approach dampen the potential for significance and impact.
GWG Votes	**Is the rationale sound?**
Yes: 12	• The project is based on a cutting-edge technology that uses AI to predict a combination of transcription factors called cell fate determinants (CFDs) to convert GBM directly into DC-like APCs. The scientific premise is supported by high-quality preliminary data. Also, there are publications of applying a similar approach in AML. • There is a strong justification of combining a CFD vector with a checkpoint inhibitor therapy. • Preliminary data are strong and provides a proof-of-concept using a lentiviral expression system for CFD delivery to tumor cells. • The clinical benefit of current immunotherapies in GBM is limited which could be due to the immunosuppressive tumor microenvironment. Reprogramming the GSCs to antigen presenting cells might reheat the tumor microenvironment and activate antitumor immunity. • The oncolysis and the fate conversion of GSCs might have synergistic effects for improving the therapeutic efficacy. The potential to translate this as an off-the-shelf product will be beneficial to GBM patients. • The proposed project is uniquely enabling for the advancement of genetic therapies. • The preliminary data support the expertise of the team to develop and investigate the proposed therapeutic strategy. The main novelty of this proposal is the in situ reprogramming of GSCs into APC-like cells with antigen presentation and cross-presentation functions. • The PI's team has successfully reprogrammed the experimental cells ex vivo (data shown), but the success rate of in situ reprogramming remains questionable. • Most of the preclinical tumor models used are not able to reflect the heterogeneity of GBM, which might impact the success rate of in situ reprogramming. • The project has some risks, in that in vivo preclinical data are missing, and it is unknown if the virus phage can penetrate tumor cells in vivo. • The rationale is sound. Oncolytic virus vectors have been in the clinic in phase 1 and 2 trials, but there have been challenges and these approaches have failed in melanoma.

No: 2	• The outcomes of previous clinical studies with oncoloytics in GBM and melanoma diminishes enthusiasm. • There are concerns over the immunogenicity of HSV and on the potential need for boosting with additional vector. • There is a lack of preliminary data showing intratumor reprogramming in vivo, so at the current time the feasibility of in vivo efficacy is low.
GWG Votes	**Is the project well planned and designed?**

Yes:
13
	• The project is well designed and logically progress from testing HSV-based CFD constructs in murine and human GBM cells and then in syngeneic and humanized GBM models in mice.
	• The experiments are well-controlled, with appropriate statistical justification.
	• There is a possibility that GBM-APCs would not only induce immune response to tumor-specific antigens, but also break tolerance to self antigens derived from normal proteins expressed in GBM cells.
	• The applicant's plan includes two aims, with two "shots on goal" with oncolytic and non oncolytic virus vectors. This redundancy is a strength in planning.
	• The candidate of the project is likely to advance to translation if it is proven to be effective given that this approach has been used clinically.
	• The PI has adequately addressed the potential pitfalls and described the alternatives for making sure this project is achievable.
	• There is attention to potential pitfalls and alternative approaches. However, there are a few weaknesses in approach as stated below:
	  ◦ GBM cells are designed to express ovalbumin as a model antigen. That's a good way for studying T cell response with a defined specificity. However, it'd also be important to test this new therapy against parental GBM cells without ovalbumin.
	  ◦ The proposed humanized models are unlikely to be informative in this project.
	• The proposed experiments and analyses to evaluate the product in vitro, in vivo, and in silico are relevant. Yet, it would be beneficial to have a direct experimental comparison between the proposed therapy and currently used related therapies.
	• The application requires additional in vivo studies to support the premise and feasibility.
	• It is not clear how the induced immune response will be maintained/boosted. Since the HSV vector is immunogenic, a heterologous prime-boost strategy could be considered.

No: 1	*none*
GWG Votes	**Is the project feasible?**
Yes: 14	• The proposed milestones and expected project outcome are logical and likely to be achieved within the proposed timeline. • Given the experience of the scientific team and the proposed experiments, the project can be accomplished in the proposed timeline. • The PI and their team are well qualified for this project. • The team has access to all the necessary resources to conduct the proposed activities. • The budget is appropriate. • The application includes strong preliminary data on reprogramming ex vivo. • There is a translational path forward for this product. • This product follows a precedent path, with viral oncolytic phages already in the clinic. • The product is scalable and can be commercialized.
No: 0	*none*
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 14	• The project plan and design adequately address and account for the influence of race, ethnicity, sex and gender diversity.
No: 0	*none*

Application #	DISC2-14915
Title (as written by the applicant)	An integrated microphysiological system to interrogate obesity-associated cardiac disease
Research Objective (as written by the applicant)	Develop an integrated cardiac-adipo-vascular microphysiological system (MPS) to addresses the proinflammatory consequences of obesity driven cardiac disease states.
Impact (as written by the applicant)	Development of stem cell models that accelerate the search for effective pharmacological interventions against obesity-associated heart failure.
Major Proposed Activities (as written by the applicant)	• To develop robust differentiation protocols for isogenic hiPSC-derived cardiac, adipose, and vascular for individual MPS. To study obesity and inflammation driven cardiac and endothelial dysfunction. • Development and testing of Microphysiological Systems (MPS) capable of supporting function and assessment of individual adipocyte, cardiomyocyte, and endothelial cell systems. • To functionally integrate cardiac, adipose, and vascular MPS (CAV-MPS) capable of the rapid and modular analysis of whole systems by integrating individual MPS for long-term culture. • Develop integrated CAV-MPS capable of real time monitoring of cardiac muscle function, endothelial permeability, and adipocyte metabolic responses. • Assess tissue-specific functional responses of the CAV-MPS to obesity, inflammation, and drug challenges.
Statement of Benefit to California (as written by the applicant)	The obesity epidemic is one of the greatest public health challenges faced by California and is a major cause of heart failure (HF). Therapeutics to treat obesity-induced HF are extremely difficult to find due to inadequate methods for screening promising drugs. We address this need by developing stem cell models that accelerate the search for effective pharmacological interventions against HF and cardiovascular disease. Ultimately, our work will improve the health of Californians with HF.
Funds Requested	$807,000
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: 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	81
Median	81
Standard Deviation	5
Highest	93
Lowest	70
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	3
(1-84): Not recommended for funding	11

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 14	• A multi-tissue integrated microphysiological system (MPS) comprised of the hiPSC-derived cardiomyocytes (CM), fibroblasts, adipocytes, and endothelial cells (EC) will serve as an in vitro tool for analyzing interactions between epicardial adipose tissue (EAT) and cardiac muscle, which in obese individuals are responsible for the heart (HF) failure and coronary arterial disease (CAD). • The multi-tissue MPS will be used for mechanistic studies of these interactions and for identifying therapeutic compounds for treatment of HF and CAD. This project is significant and will impact an unmet medical need. • The project specifically targets obesity-induced cardiac disease, which is one of the significant public health challenges. The CAV-MPS is designed to address the bottleneck in obesity/cardiac research by developing human-relevant tools for understanding and treating cardiovascular dysfunction, especially heart failure (HF) and coronary artery disease (CAD). • The project addresses a major unmet need for a disease (obesity-associated cardiovascular disease). • Applicants propose that local factors affect cardiomyopathy. • The expected candidate, the CAV-MPS, is designed to accelerate the search for effective pharmacological interventions against obesity-induced HF and CAD. By employing human-induced pluripotent stem cell (hiPSC)-derived cardiomyocytes, cardiac endothelial cells, cardiac fibroblasts, and adipocytes, the system aims to create a human-relevant model that can empower the search for novel patient-specific treatments. • An integrated microphysiological system to interrogate obesity-associated cardiac disease by having various cell types in these chips. • The proposed tool to study this disease, a microphysiological system (MPS) that includes iPSC-derived disease-relevant cell types, is novel and has potential for discovery. • The candidate is timely, especially since the FDA no longer requires the use of animals in preclinical studies for new drugs, paving the way for complex in vitro models like MPS to dominate the preclinical drug discovery landscape.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• The project is based on a sound scientific rationale that human MPS systems can faithfully recapitulate many aspects of human physiology, and that they can be adapted to mimic complex physiologically relevant multi-tissue interactions. • The proposed project is based on sound scientific rationale. The project aims to develop an integrated cardiac, adipose, and vascular Microphysiological System (CAV-MPS) to interrogate obesity-associated cardiac disease. • Strong preliminary data, system can be used to study several/multiple cell lines. • This will be a tool, FDA welcomes the use of these types of systems for screening and drug targeting. • The rationale of studying cell-cell interaction in an MPS is sound, and the system has advantages over other model systems: it is human, it can theoretically recapitulate physiological processes better than other 2D or 3D culture systems, and enables both molecular and cellular measurements as well as physiological phenotypes such as contractility. • The proposal would have been stronger if the applicants discussed the wider utility of the system for studying other proposed mechanisms of obesity-associated CVD that do not involve EAT, such as hypertension, hyperlipidemia and systemic inflammation, which can readily be modelled to the MPS. • General enthusiasm for the proposal.

No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 14	• The project is appropriately planned with all needed controls in place. The proof-of-concept experiments presented in the preliminary results section and those planned for the study will likely advance this project into translational pipeline. • The project is well-constructed and of high quality. It leverages cutting-edge technologies, including single-cell RNA sequencing, hiPSC-derived cells, and microphysiological systems (MPS). • Some concerns about the complexity of the system. • There are no sufficient alternative approaches presented.
No: 0	• There is a clearly-defined path to translation should the project succeed. • While it was clear that the PIs were leaders in their field, the review group was concerned with the complexity of the system and the lack of a clear division of labor. It seemed that a first-year graduate student would carry out the bulk of the projects, supported by two postdocs between the groups of the two applicants. This strategy seems risky for a wholly new endeavor. • Milestones 1 and 2, the generation of cell lines and introduction to the MPS, are already well-established in the laboratory, and it seems much more important to focus on the identification of a common media, and then test how cellular phenotypes may have changed in this new medium in the context of the MPS before proceeding with milestone 4. The review panel felt that this is where the bulk of the work lies to generate a well-functioning and well-characterized MPS. • Deeper molecular characterization of the constituent cell types seems warranted before moving ahead with experimental manipulation.
GWG Votes	**Is the project feasible?**
Yes: 14	• The proposed milestones are logical and should be achievable within the proposed timeline. The team possesses a high level of complementary expertise and has abundant experience in the field of proposed study. They are ideally suited to carry out the project. • The team and post-docs have sufficient expertise. • This project may be too complicated because it requires making many different types of cells from iPSCs to build the model. • Failure in differentiating one of the cell types, such as macrophages, will result in a failure in the whole project. • A risk is a complicated system with a very heterogeneous environment. It may be hard to find the culture system that supports all these cells.
No: 0	• As discussed above, the project could indeed work but there were major concerns about the path chosen to achieve this result.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 14	• The project accounts for the influence of race and ethnicity on HF and CAD. Currently available in vitro screening models for therapeutics to treat these diseases often fail to take into consideration race and ethnicity. The proposed project will overcome this limitation by utilizing hiPSC lines from a cohort of patients from diverse racial and ethnic backgrounds. • The project plan and design explicitly address and account for the influence of race, ethnicity, sex, and gender diversity. The proposal emphasizes the implementation of a diversity of hiPSC patient lines representing a diverse background into the drug testing/discovery pipeline. • The plan includes the use of patient lines that reflect California's racial distribution and both sexes. • The project outcomes aim to inform the development of a product that serves the unmet medical needs of the diverse California population. The proposal recognizes the disproportionate effects of obesity-associated diseases, including heart failure (HF) and coronary artery disease (CAD), on Non-Hispanic Black and Hispanic adults. • addresses a prevalent problem impact of CVD and Obesity on black/ hispanic in CA population single male cell line

	• The applicants both clearly support DEI principles in their own research groups. • It is sensible to select 1-2 well-established cell lines before expanding this to include others from diverse genetic backgrounds and sex chromosome status, but it would be helpful to know how much this will be prioritized over other studies (e.g. addition of drugs), especially since results from a single cell line could be misleading.
No: 0	*none*

Application #	DISC2-15164
Title (as written by the applicant)	Oral mRNA-based gene therapy to treat Microvillus Inclusion Disease
Research Objective (as written by the applicant)	Oral mRNA-based gene therapy for Microvillus Inclusion Disease (MVID). Candidate product is an oral formulation of mRNA encoding for the MYO5b protein delivered to the intestinal epithelial cells.
Impact (as written by the applicant)	The primary indication is Microvillus Inclusion Disease. Proof-of-concept would resolve the technical bottleneck needed to treat congenital diarrheas and enteropathies (CODEs).
Major Proposed Activities (as written by the applicant)	• Synthesize and characterize mRNA encoding for MYO5b and formulate in oral lipid nanoparticle • Proof-of-concept in MVID mice models and establishment of a pharmacodynamic response that can be used in clinical trials • Validate oral gene therapy approach in patient-derived organoids
Statement of Benefit to California (as written by the applicant)	Particella has developed an oral lipid nanoparticle based formulation for delivery of mRNA. There are no currently available oral mRNA technologies and validation of the technology will provide California with a strong and unique position in the gene therapy field. This will create jobs and provide cash inflows to the state. In addition to the economic benefit, identification of a new therapeutic modality for MVID will be life-changing for patients, their families, and caregivers.
Funds Requested	$1,498,637
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	6
Highest	90
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	4
(1-84): Not recommended for funding	11

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 15	• The proposed studies are aimed at developing a genetic therapy to treat Microvillus Inclusion Disease (MVID) and restore function to microvilli. It is a high morbidity, high mortality disease that results in total intestinal failure due to mutations in the MYO5b gene. Because the only available and curative treatment is small bowel transplantation, which has a high mortality rate, the proposed technology is likely to result in a candidate that could impact an urgent and unmet medical need. • Microvillus Inclusion Disease (MVID) is a rare congenital diarrheal disease with serious consequence due to the requirement for intravenous nutrition. The applicant's oral LNP technology, if it can successfully deliver Myo5b to the intestinal epithelium, will be a life-saving therapeutic to otherwise untreatable MVID patients. • Proof-of-concept for MVID would suggest that a similar type of approach could be used to restore function and deliver a disease-modifying treatment for other rare monogenic diseases of the gastrointestinal (GI) tract for which the causative gene is known. Such a technology could significantly address a critical bottleneck to the development of genetic therapies to a wide variety of GI disorders for which there are few if any treatment modalities, including congenital diarrheas and enteropathies. • The potential for impact is dampened by concerns about the GI stem cell component (which is not addressed sufficiently), immunogenicity/toxicity of daily oral LNP, and the potential high dose/cost of clinical treatment.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• The overall strategy, methodology, and analyses are well-reasoned and appropriate to accomplish the milestones of the project. It is timely, important, innovative and has a high probability of success in treating a devastating disease. Risk is moderate and somewhat offset by preliminary data in support of the feasibility for each of the three milestones. Development of the applicant's proprietary LNP allows for the delivery of mRNA to the site of injury, which is the intestinal epithelial cell. • The preliminary data are compelling and supportive of the proposed project and each of the three milestones. They support the feasibility for a successful outcome. Critical to the study is to optimize LNP delivery to intestinal epithelial cells and endosomal release for protein expression, which appears to have been accomplished. The data presented on MVID patient-derived enteroids/organoids is particularly strong and underscores the probability of a successful outcome. • Preliminary data indicate that the LNP can be delivered and have efficacy, but the persistence of efficacy is not known. • The preliminary data are insufficient.
No: 1	• Proof of concept delivery experiments are shown in normal bowel mice but only show a benefit in a narrow window. The MVID model likely comes with abnormal/irritated gut morphology that might significantly impact the uptake of LNP. Therefore, the lack of Myo5b transfection and translation efficiency in the MVID model or equivalent mouse dampens the enthusiasm for the proposed approach. • Oral delivery of LNP seems feasible based on some preliminary data. However, the meaningful benefit for MVID comes from durable and long-lasting efficacy, which will likely be challenging with this type of transient mRNA delivery-based approach. Also, the magnitude of 10% restoration of correctly expressed Myo5b sets a high bar, thus highlighting a need for preliminary data to support the application. The applicant recognizes this, but these points should be more directly addressed. • The applicant explains the need to target intestinal stem/progenitors for enhancing durability but it is not clear why this would enhance the efficacy of their product. This rationale needs additional clarification.
GWG Votes	**Is the project well planned and designed?**
Yes: 13	• The project is appropriately planned and designed to achieve the expected outcomes, including proof-of-concept data for a product candidate that is ready to advance to translational studies. The applicant has already generated strong preliminary data in support of their success within the 24 month timeline. In addition, the product therapeutic

	could potentially be used for the treatment of a wide variety of monogenic enteropathic diarrheal disorders. • This is a well-constructed, quality project with low risk. The experimental design is logical and supported by strong preliminary data. Potential pitfalls and alternative approaches are considered; and the project could be completed within the timeline of 24 months. Milestone 1 will be carried out by the team at the applicant's institution, and milestones 2 and 3 will be completed by a world-renown team at a collaborating institution. A successful outcome will allow advance to IND-enabling studies and FDA approval. • Overall plans are well-structured and cover critical experiments to nominate the candidate LNP based product. • Potential problems and alternative approaches for the three milestones are presented, albeit not in great detail. This, in part, is due to supporting preliminary data for each of the milestones. The biggest challenges to success in rescuing MVID mice is expressing enough Myo5b protein in the correct intestinal epithelial cells over a wide-enough distribution to increase survival of the mice, reduce water content and ameliorate weight loss as a proof-of-concept for the candidate. • Some details around the dosing scheme are missing in the PD studies. Related to this, given that oral LNP might require extensive dosing and repeated administration, it would be ideal to determine the maximal tolerated dose (MTD). • In their mechanistic studies, the applicants explored only phenotypic rescue. However, the restoration of correctly expressed Myo5b proteins requires a series of biological events such as translation, localization, and degradation. Such mechanistic steps will be vital to understand the potential mechanisms of rescue by exogenously delivered Myo5b localization. Therefore, additional molecular biology assessment will strengthen the proposal.
No: 2	• The applicants should provide more detail on whether repeat therapy will be needed, and the persistence of efficacy, to justify their approach. • Some aspects of the proposal are underdeveloped, and the organization could be improved.
GWG Votes	**Is the project feasible?**
Yes: 14	• The proposed milestones and project outcome are logical and likely to be achieved within the proposed timeline of 24 months. This is based on strong preliminary data, expertise within the collaborating teams and the feasibility of targeting intestinal epithelial cells. The concept of gene therapy to the gut and the possibility that a similar approach could be applied to other CODE monogenic diseases is transformative. The candidate would definitely impact an unmet medical need. • The PI has expertise in gene therapy. The collaborators, and other researchers are all well suited to the project, providing complementary and integrated expertise. A key element of the research plan, and its success, is the involvement of a collaborating laboratory in which the role of the MYO5B mutation in MVID was discovered and characterized. • The timelines for Milestones 2 and 3 are overly ambitious. The applicant team has a substantial track record in MVID.
No: 1	• The application lacks sufficient information to support oral delivery of mRNA via their proposed mechanism. • Because the persistence of mRNA efficacy for these diseases is unknown, the applicants should consider more studies of the microbiological disease and therapeutic process rather than focusing on a presumably short-acting genetic therapy.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 15	• MVID is a rare disease and therefore it is difficult to address and account for the influence of race, ethnicity, sex and gender diversity. Simply stated, the largest concentration of MVID cases is found in the Navajo Nation in addition to a higher incidence in certain Middle Eastern populations. The applicant organization remains committed to advancing the drug to the clinic and will make every effort to recruit a study population with racial/ethnic, sex, gender and age diversity. • The largest concentration of MVID cases is found in the Navajo Nation. MVID patients living in Navajo reservations do not undergo small bowel transplantations due to religious and cultural prohibitions. This eliminates any treatment options for those patients. Other

	underserved groups with high incidence include certain Middle Eastern and Turkish populations. Efforts would be made to recruit the affected minority populations in CA for future clinical studies with the understanding that MVID is very rare. • MVID is an extremely rare disease; therefore difficult to cover the broad spectrum of DEI. However, this disease is enriched in the Navajo Nation, wherein organ transplantation is culturally unacceptable. Having said that, this oral LNP methodology is poised to deliver equitable and accessible options to such minority groups.
No: 0	*none*

Application #	DISC2-15113
Title (as written by the applicant)	Self-delivery of a tissue-targeting CRISPR-Cas9 fusion protein therapeutic for the treatment of a rare liver disease
Research Objective (as written by the applicant)	A tissue-specific gene-editing therapeutic will be developed to treat a liver disease. The therapeutic platform can be applied to unmet medical needs across a multitude of tissue and cell types.
Impact (as written by the applicant)	This condition is a genetic disease causing debilitating attacks, pain, and serious neurological complications. This therapeutic could dramatically improve patient quality of life and mental health.
Major Proposed Activities (as written by the applicant)	• Select engineered ribonucleoprotein (RNP) constructs • Demonstrate selective uptake of RNP constructs into hepatocytes • Demonstrate on-target editing of RNP constructs within hepatocytes • Demonstrate amelioration of disease phenotypes in a human cellular model • Demonstrate target knockdown, biodistribution and safety in wild-type mice • Demonstrate disease modification and on-target editing in a murine disease model
Statement of Benefit to California (as written by the applicant)	The genetic disease targeted by this therapeutic predominantly impacts women, across all ethnicities. Patients suffer debilitating pain and several acute attacks each year, and diagnosis can take 10+ years, despite a simple urine diagnostic. The State of California has one of 6 leading centers for this condition in the US, a significant population of current patients in CA, and others that are under-diagnosed. This therapeutic would address a significant unmet medical need for these patients.
Funds Requested	$2,003,805
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	7
Highest	85
Lowest	65
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	4
(1-84): Not recommended for funding	11

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 14	• The proposed technology could conceivably result in a candidate that impacts an unmet medical need. The product is a liver-targeting CRISPR-Cas9 protein-based therapeutic designed to selectively inactivate ALAS1 in the liver, and specifically, hepatocytes. • This liver disease can manifest as acute neurovisceral attacks with debilitating abdominal pain and life-threatening neurological complications. The current standard of care is a double-stranded siRNA therapeutic. It reduces but does not entirely prevent attacks. The applicant will treat this disease via self-delivery of the CRISPR protein to reduce attacks in patients. • The proposal aims to demonstrate that a single intravenous administration of highly liver-selective fusion protein to provide a long-term cure this disease. As this liver disease lacks a complete cure for devastating neurological symptoms, the proposal brings a transformative impact on clinical care. • As current standard of care siRNA product is a temporal therapeutic, a gene editing approach will be attractive option. • Drug already exists but this drug needs to be taken daily - the proposal would be an advance on delivery. • Novel but other therapies are in development. • May not be a critical unmet need and may not need to use the CRISPR approach.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• The proposed project is based on sound scientific rationale that includes (i) engineering a diverse set of RNPs optimized for serum stability, hepatocyte targeting, endosomal escape, nuclear localization, and optimal on target editing in human hepatocytes; (ii) confirmation of reduced target levels and activity in diseased human hepatocytes; and (ii) mechanism of action, biodistribution, and safety in a valid clinically relevant mouse model. • Critical to success of the project is the efficient targeting to the hepatocytes. The studies are designed to develop a first-in-class CRISPR-Cas9 protein-based therapeutic to selectively inactivate the target based on cell type specificity and self-delivery. • The project leverages CRISPR-Cas9 technology, a well-established method for genome editing, to target a clinically validated target for this liver disease. • This can target 100% hepatocytes, better than the drug that is available. • Yes, particularly because the therapeutic reduction of the target is already proven to be clinically meaningful. However, most preliminary data is based on molecular biology approach predominantly using immortal liver cancer cells that is irrelevant for in vivo hepatocytes, making this proposal high-risk and high-reward. • May need some more preliminary data. • No preliminary data on in vivo editing of liver cells. How does the fusion protein pass through the blood vessels and enter liver cells?
No: 1	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 14	• The project is appropriately planned and designed to achieve the expected outcomes, including proof-of-concept data for a product candidate that is ready to advance to translational studies. No allogeneic cell components are involved. The applicant has already generated strong preliminary data in support of their proposal. In addition, the product therapeutic could potentially be used for the treatment of a wide variety of monogenic liver disorders. • This is a well-constructed, quality project with low risk. The experimental design is logical and supported by strong preliminary data. Potential pitfalls and alternative approaches are considered. The research plan would suggest that the project could be completed within the timeline. Milestones 1-4 are designed to confirm the precise activity of lead candidates and milestones 4-6 will assess their mechanism of action, biodistribution, and early safety profiles. • The applicants provide alternative approaches for the situation that gene editing components are not stable in serum. • It could fulfill an unmet need, but not a huge unmet need.

	• Some concern around the available data. • No in vivo data and only use of immortalized cells, no benchmarking provided.
No: 1	• More attention should be given to the in vivo optimization for editing efficiencies. • Proposed components using in vitro molecular biology toolsets are well-designed. However, in vivo therapeutic efficacy design only evaluates short-term benefits upto 3-7 days. This will be concerning given that the applicant intends to develop a better product that the current standard of care cannot deliver. An additional point of concern involves the impact of hepatocyte renewal. • As the liver is a highly regenerative organ, if the fusion protein delivery puts stress on hepatocytes, it might be possible that non-stressed hepatocytes will replace cells and dominate for a certain period of time. These aspects can be experimentally tested but are not well planned. • It would be preferable to conduct a head-to-head comparison against the standard of care, as this is an approved therapeutic.
GWG Votes	**Is the project feasible?**
Yes: 13	• The proposed milestones and project outcome are logical and likely to be achieved within the proposed timeline of 18 months. This is based on strong preliminary data, expertise within the team and the feasibility of targeting the product to hepatocytes via the unique asialoglycoprotein receptor. The concept of gene therapy (i.e., editing) without requiring a nanoparticle delivery is both innovative and exciting. The RNP complex could conceivably target all hepatocytes in vivo. • The PI and team appear to be well suited to the project. They provide complementary and integrated expertise to the study and at least three TBD scientists and a research associate are included in the list of personnel. In addition, intellectual support from one of the team members, an expert on CRISPR technology, is a major advantage for the team. • Feasible and well designed. • There is no preliminary data for in vivo gene editing. What if the Cas9 and sgRNA cannot pass through the endothelium? • Some concern that these assays and technology will actually work - some limitation to the data. • Milestones 5, 6 will be very tight, with ambiguity around success. More clinical expertise will be preferable as no clinician-scientists are directly engaged in the proposal. • Liver expert is missing.
No: 2	• The delivery of this candidate has not been demonstrated to the liver in vivo. Therefore, the feasibility of the animal experiments is low, given the very low genome editing efficiencies shown in vitro.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 15	• Overall, yes, the project plan and design address and account for race, ethnicity, sex and gender diversity. The disease disproportionately affects women across all ethnicities, and accounts for as many as 80% of cases. The founders are entirely committed to DEI at their respective institutions. The applicant organization is committed to making the therapeutic available and accessible to all underserved patients. • The project recognizes that the disease disproportionately affects women and plans to include diverse ethnicities in clinical studies. • Well discussed. • The applicant emphasizes patient advocacy and education but does not specifically detail how perspectives and experiences from the population will be incorporated.
No: 0	*none*

Application #	DISC2-14890
Title (as written by the applicant)	Transplantation of excitatory V2a interneurons to promote motor function recovery after spinal cord injury
Research Objective (as written by the applicant)	The objective is to generate enriched human spinal cord V2a excitatory interneurons that can enhance descending neuronal relay formation and motor functional recovery after spinal cord injury.
Impact (as written by the applicant)	As there are currently no effective therapies for spinal cord injury (SCI), the proposed studies will develop a novel and more specific cell product that will improve motor function for SCI patients.
Major Proposed Activities (as written by the applicant)	• Modify the current protocol to generate spinalized or spinal cord V2a (scV2a) interneurons by generation of spinalized neural stem cells followed by V2a specification. • Single cell sequencing to characterize scV2a interneurons at the molecular level. • Generate a reporter cell line that depends on Chx10 expression for monitoring scV2a neuron differentiation, maturation, and integration. • Optimization of parameters of scV2a interneuron transplantation in vivo after SCI • Investigate whether transplanted scV2a excitatory interneurons successfully form descending neuronal relays. • Investigate whether transplanted scV2a excitatory interneurons successfully promote motor function recovery.
Statement of Benefit to California (as written by the applicant)	SCI affects approximately 300,000 people in the U.S., with more than 20,000 new injuries per year. People with SCI often endure decades of severe disability, with staggering physical, emotional, and financial costs. The first year of treatment alone is $1 million for a quadriplegic patient. Better treatments are needed, and even a modest increase in functional capacity (1-2 spinal levels) can produce meaningful improvement in quality of life and cost savings for California.
Funds Requested	$1,754,749
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	80
Lowest	70
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project hold the necessary significance and potential for impact?

Yes: 13	• The proposal addresses an unmet need with an easy-to-follow proposal.
	• The overall goal is to optimize a protocol to increase the population of V2a cells from 6% of transplanted cells to 20%. The applicants rationalize that spinal cord specific V2a interneurons are more suited to produce mature, differentiated population. They also aim to enhance survival and maturation of these cells in vivo in SCI models by identifying supportive small molecules, growth factors and key time points along the differentiation process.
	• The application is focused on potentially enhancing a product that is moving toward clinical trials in SCI.
	• The underlying hypothesis that improvement could be further enhanced by enriching the population of grafted neurons with excitatory spinal motor interneurons, and specifically V2a (also known as Vsx2 or Chx10- expressing) spinal interneurons is reasonable and has already been proposed in a 2022 publication. This same group also showed that mouse neural progenitor cells enriched with V2a interneurons can promote repair after cervical SCI in their 2018 publication. Thus, the innovative step in this proposal is limited.
	• Although the concept is not novel and transplantation of these cells has been previously shown by other researchers and the applicants in animals with SCI, there are several strengths in this proposal. Furthermore, SCI poses significant health concern and as such this project addresses an unmet need to develop new treatments for SCI.
	  ◦ Strengths include use of human cells, generation of spinal cord specific V2a, use of targeted growth factor supplement based on scRNAseq data to enhance graft survival, and trans-synaptic neuronal labeling to assess connectivity of the engrafted cells with host supraspinal motor neurons and local spinal motoneurons. The use of the C5 cervical SCI model that represents a more prevalent and challenging type of SCI is another strength.
	  ◦ Thus, the proposed project holds the necessary significance and potential for impact. However, the work also has some limitations that are discussed in the following sections.
	• The advancement of transplantation of NSC into spinal cord, which provides the basis of this potential enhancement, has been supported by prior funding to this group with two publications reported. However, studies to assess the Minimum Effective Dose (MED) and Maximum Tolerated Dose (MTD) that support proof-of concept and function have not yet been completed, thus the underlying hypothesis of enhancing the outcomes seems premature.
	• The plan for translation is well developed, although the use of immunocompromised rats limits translatability to clinics.

No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• The proposal is rationalized and supported by published data from the applicant's previous work and that of others. The importance of V2a interneurons as a target for cellular therapies for SCI is clearly rationalized. • This proposal was built on a sound scientific rationale and preliminary data. The preliminary data are extensive and supportive of the proposal. • The rational is sound and based on data by others using mouse cells. However, whether increasing the proportion of V2A cells compared to other cell types will impact outcomes in humans is not yet clear. • For most key techniques, the applicants have provided proof-of-concept data to suggest technical feasibility within this group.

	• Since protocols to generate highly enriched human V2a interneurons have been established, it would have been important to demonstrate that increasing the presence of such cell in a human neural stem cell graft is indeed beneficial. Such data are not provided, and it thus seems that optimizing protocols is premature.
No: 1	*none*
GWG Votes	**Is the project well planned and designed?**

Yes:
11
	• The proposed experiments are properly designed, utilizing advanced methodologies to effectively assess the survival and biodistribution of engrafted cells and track their interactions with the host network. The proposal is well-written and detailed and easy to follow.
	• The applicants have proposed several transplantation paradigms to test various combination of scNSC and scV2a cells in SCI in order identify the most suitable strategy that would allow survival and maturation of engrafted V2a in the lesion. Overall, the proposed project is logical and represents a thorough transplantation study with all necessary techniques and assessments. However, several points about the project design are concerning:
	  ◦ First is exclusive use of immunocompromised rats. Although this is needed to identify any potential risk for tumorgenicity as scNSCs are derived from pluripotent stem cells, the applicants could use a small group of immunocompromised rats for this verification. The model does not match the reality of human trials. Even if scV2a neurons survive in immunocompromised rats, this does not mean they will survive in human applications. Since a main goal of this funding mechanism is ultimate translation of preclinical studies to clinical testing, this is a missed opportunity for this project to go through all these experiments only with immunocompromised rats.
	  ◦ The second point is the use of PSCs when direct reprogramming of somatic cells to NSCs is a more logical approach for translational purposes. These two aspects reduce enthusiasm for this proposal.
	  ◦ Another minor point is the quality of the immunohistochemistry of transplanted cells in the spinal cord. With the overexposed signal of the engrafted cells, is hard to get a clear picture on their biodistribution and survival.
	• Potential pitfalls are identified and alternative approaches are presented.
	• The project is well-planned with appropriate proof of concept data. However, while the applicants (well) argue about the inclusion of only female rats, they later go on to say that subsequent conclusive experiments will include both male and female animals. The data or results that the applicants will use to change approaches is not clear.
	• It is not clear when, or for which experiments, male rats will be used. The applicants should state the number of animals in each group and provide power calculations, as well as details on the ages of animals that will be used in each experiment.
	• The applicants are only using immunocompromised and single sex (female) animals. Although they are assessing efficacy, there is no consideration of safety assessments, as well as no power calculations and no details on animal age.
	• The in vivo efficacy of V2a-enriched NSC should perhaps have priority over optimization protocols, especially in light of protocols that have already been published to result in V2A neurons. In other words, Milestone 1-3 might be more relevant if Milestone 5 and 6 do not show the desired effect.
	• Protocols for generating human V2a interneuron from human pluripotent stem cells have been established and it is not clear to what extend the current proposal would be superior to prior work by others.
	• A major weakness is the use of a single embryonic cell line.
	• Based on their data, it seems these cells have occupied/invaded the entire spinal cord instead of integrating with the host circuit.

No: 3	• The applicants are only using immunocompromised animals and missing experimental details for in vivo experiments. • Translation may be an issue with the use of only one ES cell type.
GWG Votes	**Is the project feasible?**

Yes: 13	• The project is well-planned and presented. The team is highly qualified and includes some internationally renowned experts. • The proposed project has high technical feasibility given the ample experience of the team, who are leaders in this field, and highly qualified to propose and conduct this research. They have been collaborating for a long time and have published together. This line of research is their core expertise. • The three labs have all the resources to conduct SCI preclinical experiments as well as transplantations. They are also supported by other collaborators and centers for the scRNAseq, genomic and bioinformatic aspects of the project. • The team is very experienced. • With regards to the lab personnel, a lab supervisor (5 months/year) will help with stem cells in vitro and one full time technician will help with all in vivo aspect of the project and technician. If PIs are not participating in the in vivo work, and only one technician doing all of the SCI models, transplantation, and AAV injections, as well as all animal care, behavioral, neuroanatomical, and histological assessments, then it is not feasible. • The budget for lab supplies seems to be low for the proposed experiments, in particular scRNAseq, which is usually expected to have a higher cost than what is allocated. • The project is overall feasible but potentially understaffed. • Overall yes, but there is a missed opportunity to try and work with other cells lines.
No: 1	*none*
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 14	• All populations would benefit from a cell therapy for SCI, although costs for such a treatment might be prohibitive for some. • The applicants have discussed race, gender, and ethnicity in relation to SCI. However, their DEI statement seemed rather general. • Eventually both sexes will be studied, but initially the focus is on female animals.
No: 0	• The applicants have discussed the disparity in the incidence of traumatic SCI in certain race, gender and age groups. They argue that the focus of their research on developing treatments to restore function addresses some aspects of the existing disparity as it is not based on access to high end medical care. • However, this rationale is not convincingly addressing DEI as the proposed stem cell therapy, and all required associated stem cell preparation and surgical procedures are not necessarily an accessible type of treatment to everyone due to the associated cost. Thus, more work is needed to appropriately identify strategies to address DEI in these types of clinical interventions. • The proposed plan to start strictly with female animals, even though males sustain higher SCI, is understandable due to practical issues with managing bladder dysfunction in male animals and as a strategy to reduce animal use. However, sex is a biological variant in neurological conditions not only due to prevalence but also due to hormonal differences. The applicants could use a mix of male and female animals with their targeted sample size to identify any potential differences. This would be an edge to this study that is designed for translational consideration. • Applicants also use one female embryonic cell line, but propose to expand in the future to males and various ethnicities. This is a potential weakness at this stage, as the use of more than one cell line could strengthen translational reproducibility of this approach. Moreover, use of directly reprogrammed somatic cells (like blood) for NSCs would be a more logical and advantageous candidate product to meet accessibility.

Application #	DISC2-14937
Title (as written by the applicant)	Optimizing stem cell-derived pancreatic beta cells with parathyroid-inspired supportive niche
Research Objective (as written by the applicant)	Improved stem cell derived pancreatic beta cells using parathyroid gland-inspired supportive niche
Impact (as written by the applicant)	Shorten the maturation time and improve survival of stem cell derived beta cells for more effective treatment of long-standing type 1 diabetes
Major Proposed Activities (as written by the applicant)	• Define optimal composition of vascular cells that enhances in vitro maturation of human stem cell-derived beta cells • Evaluate top vascular cell formula in supporting stem cell-derived beta cell in diabetes reversal in preclinical models • Determine if vascular cell-enhanced stem cell-derived beta cells can be further supported using parathyroid tissue • Develop a cocktail that mimics parathyroid gland in supporting islet transplantation • Test parathyroid cocktail in supporting stem cell derived beta cells • Select clinically eligible stem cell line for engineering stem cell-derived beta cells
Statement of Benefit to California (as written by the applicant)	Diabetes affects 3.2 million Californians with annual healthcare costs approaching $40 billion. Patients with T1D and many with T2D benefit from insulin therapy. By improving the efficacy of stem cell-derived beta cell replacement therapy, this study aims at developing an effective curative therapy from a renewable source. The technology to be developed may also invigorate biotech development in this field in California.
Funds Requested	$2,764,200
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: 80

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

Mean	78
Median	80
Standard Deviation	5
Highest	85
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	3
(1-84): Not recommended for funding	12

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 15	• The project aims to develop a therapeutic product that could significantly impact the treatment of type 1 diabetes (T1D). The proposed technology focuses on optimizing stem cell-derived pancreatic beta cells with a parathyroid-inspired supportive niche. • The therapeutic product is intended to replace lost pancreatic beta cells in patients with long-standing T1D, addressing the challenges of limited beta cell supply, the need for invasive surgery, and variable efficacy. • The project's significance lies in its potential to revolutionize the treatment of diabetes by enabling access to therapy for a broader patient population who can benefit from it. • Development of a supportive vascular niche for improving survival, maturation, and function of human induced pluripotent stem cell (hiPSC)-derived insulin producing beta cells after their transplantation into the pancreas will impact an unmet medical need in the treatment of diabetes. • There is an unmet need in translational research to use stem cells to replace pancreatic beta cells. The applicant seeks to optimize stem cell-derived beta cells with a parathyroid-inspired supportive niche. • The project leverages preliminary results from the PI's laboratory suggesting that parathyroid gland (PTG) vascular endothelial cells (ECs) and pericytes, as well as PTG-secreted soluble factors, may have a superior beta cell-supportive activity. • Transplantation of stem cells for beta cell replacement in T1D has limitations that include limited survival and function. Inspired by recent findings that PTG co-transplantation with islets improves islet engraftment in the pancreas, the applicant aims to engineer the stem cell-islet niche with cells and factors that recapitulate PTG's pro-angiogenic function. • The proposal's emphasis on renewable stem cell sources and minimally invasive therapy could revolutionize diabetes treatment and make it accessible to a broader patient population, including those with type 2 diabetes. • The proposal includes specific objectives and milestones, such as selecting top-performing human pluripotent stem cell (hPSC) lines, evaluating the impact of the vascular niche on SC-beta maturation, and assessing clinically eligible niche-engineered SC-islets' survival and function.
No: 0	*none*
GWG Votes	**Is the rationale sound?**

Yes: 15	• The project is built on the strong scientific rationale that vascular cells may play an important role in the in vivo survival, maintenance, and function of transplanted islets. The preliminary data are compelling and supportive of the project. Overall, it suggests that the vascular niche improves SC-beta cell survival and function.
	• Overall, yes, though there are concerns based on the applicant's preliminary data about the quality of the SC-islets and the ability of niche SC-islets to reverse diabetes.
	• The applicant provides strong preliminary data on the use of PTG tissue to improve islet survival and vascularization, with strong proposed mechanisms.
	• Yes; sufficient data to support this work.
	• Overall, yes, with limitations:
	  ◦ The proposal does not include sufficient data on hPSC differentiation towards beta cells.
	  ◦ The animal study data presented in Figure 6 are relatively weak.

No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 10	• The proposal outlines a systematic approach to define the composition of the PTG niche by testing and comparing various cellular and protein components. The experiments are structured to provide intermediate outcome measures, such as SC maturation in vitro, cell survival in vivo, and revascularization in vivo. • The project is designed to optimize stem cell-derived pancreatic beta cells with a parathyroid-inspired supportive niche, addressing critical issues such as poor engraftment, invasive surgery, and variable efficacy.

	• The applicant acknowledges that adaptation from planar to suspension culture can constitute a heavy selection, leading to the emergence of cells with karyotypic abnormalities. To monitor this in real time, the proposal includes the use of karyotype analysis before and after adaptation and expansion. • The project plan and timeline align with CIRM's mission to accelerate world-class science to deliver transformative regenerative medicine treatments. • Overall, yes, though there are some concerns about the experimental design and the lack of supportive preliminary data. • Yes. This is a timely and needed project that can in fact translate.

No:
5
	• The plan for the project is logical. Aims 1 and 3 are appropriately designed to achieve the expected outcome of a DISC2 award.
	• However, Aim 2 - defining PTG-derived soluble angiogenic factors for a supporting niche in SC-beta engineered islets - is underdeveloped, and is unlikely to be successful, for the following reasons:
	  ◦ The results of the preliminary screen to identify factors differentially secreted by PTG vs. islets, to define a cocktail of active components from PTG-conditioned medium, are not sufficiently promising. Differences in factor expression between PTG and islets are not always apparent and are not well-quantified. Thus, this initial screen does not provide a good starting point for further investigation.
	  ◦ The proposed in vitro screens to define the composition and the dosage of individual factors in the optimal cocktail will be complex, time-consuming, and not necessarily achievable within the proposed timeline.
	  ◦ Plans for in vivo validation of the optimal cocktail need improvement. The applicant proposes to deliver the therapy in a hydrogel formulation that they have previously optimized. Unfortunately, this formulation is not described, so reviewers cannot evaluate whether it might be useful for delivery and/or preservation of factor activity in vivo.
	• Aim 1 is strong.
	• There are concerns about Aim 2. Many conditions are proposed and the undefined hydrogel increases reviewers' uncertainty about the project.
	• Aim 3 is underdeveloped.
	• Since the concentration and the release kinetics of the factors in vivo is unknown, it is not clear if and for how long they would be active at the transplantation site. To address the deficiencies of in vivo validation assays, a collaboration with a bioengineer would be useful.

GWG Votes	**Is the project feasible?**

Yes:
13
	• The specific aims and milestones are logical. The milestones under Aims 1 and 3 should be achievable, but Aim 2's milestones might not be achievable within the proposed timeline.
	• The proposed milestones and expected project outcomes are logical and feasible.
	• Overall, yes, though a major concern is that this team may not have adequate experience or success with beta cell differentiation from hPSCs.
	• Yes, but issues about the quality of the stem cell derived beta cells were raised in this review.
	• Possibly, but
	  ◦ Aim 2 may not be feasible, as PTG factors remain undefined and gel composition for delivery is not described in the application.
	  ◦ Aim 3 is underdeveloped does not adequately focus on the capability to differentiate stem cells into SC-islets.
	• This is an excellent team with the multi-disciplinary expertise needed to achieve the proposed work.
	• Regarding the special budget supplement: The proposal includes a specific aim to identify clinically compatible human pluripotent stem cell (hPSC) lines for the generation of niche-engineered SC-islets.

No: 2	• The preliminary data on longer-term diabetes reversal are not adequately convincing. • The applicant should revisit the numbers of animals in the proposed animal model studies. • Two Aims are underdeveloped.

GWG Votes	Does the project uphold the principles of diversity, equity and inclusion (DEI)?
Yes: 15	• T1D and T2D affect members of all races, genders, and socioeconomic groups. By focusing on these devastating high morbidity diseases, this project adequately accounts for the influence of these factors on public health. The project's design, especially the design of Aim 3, is directly relevant to issues of DEI. • The proposal aims to use tools that account for population diversity, dedicating efforts to test stem cell differentiation and enhancement strategies to five additional human pluripotent stem cell (hPSC) lines. • The therapeutic product aimed to be developed will address challenges to enable access to therapy by a broader patient population who can benefit from it. • Overall, yes, but proposal does not explicitly detail the incorporation of perspectives and experiences from the population that will benefit from the proposed product in the implementation of the research project. • DEI is properly discussed in this application. • The DEI response is adequate.
No: 0	*none*

Application #	DISC2-14975
Title (as written by the applicant)	Pluripotent stem cell-derived liver organoids for treatment of liver disease
Research Objective (as written by the applicant)	The proposed technology is the development of allogeneic pluripotent stem cell (PSC)-derived liver organoids for implantation into patients with liver disease as functional tissue replacement therapy.
Impact (as written by the applicant)	PSC-derived liver organoids will provide a stable and scalable source of functional hepatocytes that can be used as adjuncts or alternatives to transplantation in the treatment of liver failure.
Major Proposed Activities (as written by the applicant)	• Aim I: Identify clinically compatible pluripotent stem cell (PSC) lines that are optimal for development of therapeutic liver organoids to treat a diverse population. • Aim II: Develop a process to generate functional and safe PSC-derived liver organoids for implantation therapy. • Aim III: Test the function and safety of PSC-derived liver organoids in treating mouse models of non-fibrotic and fibrotic liver disease.
Statement of Benefit to California (as written by the applicant)	Pluripotent cell stem-derived liver organoids will provide a stable and scalable source of functional hepatocytes that can be used as adjuncts or alternatives to liver transplantation in the treatment of liver failure. This novel therapeutic will alleviate the suffering of those with end-stage liver disease and promote equitable access to life-saving functional tissue replacement therapy.
Funds Requested	$2,764,201
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	77
Median	80
Standard Deviation	4
Highest	82
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 14	• Creating functional replacement tissues that can serve as alternatives or adjuncts to transplantation in the treatment of end-stage organ failure is a critical unmet medical need. Among the most dire is the need to develop novel therapies to treat end-stage liver failure. The proposed technology is the development of allogeneic PSC-derived liver organoids for implantation into patients with liver disease as functional tissue replacement therapy and an alternative to liver transplantation. • The candidate product could potentially increase the likelihood of developing a broad stem cell-based technology that improves patient care and addresses a critical roadblock to therapy. The development of organoids and their application to regenerative medicine for a myriad of organs is potentially transformative and standard-of-care for the treatment of numerous diseases. The application of the product to genetic diseases is a further logical translation to an unmet medical need. • With tens of thousands of people dying due to unavailability of liver transplants, yes, this proposal meets an unmet need. The liver organoids to be transplanted are derived from stem cell lines, and probably cannot be generated any other way. • There is a possibility that the proposed approach can provide a benefit in a congenital inborn errors of metabolism. The application discusses the novelty of stem cell-derived hepatocytes in relation to primary hepatocyte transplantation therapy. ◦ However, the proposed disease model is a highly specialized model to apply selective pressure to engrafted transplanted cells, and the applicant needs to carefully choose the right model to assess the candidacy of the said product. • The field of end-stage liver disease conditions suffers from an organ shortage crisis highlighting the urgency to develop alternative strategies. However, it is unclear how end-stage cirrhotic conditions can accommodate the intraportal transplantation approach, which is anticipated to cause malicious portal hypertension.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• The ideal solution to solve the problem of donor organ shortage is to create an abundant supply of functional liver tissue with "off-the-shelf" availability, which can be implanted to treat patients with liver failure as clinical needs arise. It remains to be seen whether delivery and engraftment of an organoid is superior to simple hepatocytes derived from pluripotent stem cells. Those studies in the past seem not to have worked in humans with liver diseases. Although somewhat risky, it might be worth pursuing. • The preliminary data are compelling and supportive of the proposed project. However, it is focused primarily on characterization of the self-assembled organoids with the rotating wall vessels (RWV), which generates rotational cultures with laminar flow and the absence of using Matrigel. • There is good 3D structure and hepatocyte-like gene expression in the test lines, in support of the rationale. The approach to screen various stem cell lines for those which might generate broadly implantable live organoids is justified.
No: 2	• One concern is that iPSC cells may not engraft into hepatic end stage disease, but they may engraft in acute liver failure. • The clinical rationale sounds impressive and can be attributed to the excellent team. The scientific rationale suffers from a certain level of ambiguity. This is partly due to inadequacy around the product definition: e.g., what specific defects does the applicant propose to tackle with this candidate? Assuming the candidate will target end-stage liver conditions, how will ammonium and bilirubin metabolism be managed with this candidate product? • The translational pathways are unclear. For example, although Matrigel waiver protocols are commendable, this proposal utilizes lab-grade rotating wall vessel (RWV) reactors as a 3D culture method. The team responded to this concern, but it is still unclear how the RWV system can be translated into cGMP protocols (biocompatibility of the vessels, etc.), and this can be a potentially fatal flaw when it comes to translation.
GWG Votes	**Is the project well planned and designed?**
Yes: 12	• The project is appropriately planned and designed to achieve the expected outcomes, including proof-of-concept data for a product candidate that is ready for advance to

	translational studies. That said, the technology relies heavily on allogeneic cell components and it is difficult to predict how the host will respond to off-the-shelf organoids for the treatment of end stage liver disease. Any success will almost invariably involve the use of immunosuppressive agents. ● This is a well-constructed, quality project that focuses on the development of an allogeneic PSC-derived liver organoid cell preparation. The product is intended for implantation into patients with end-stage liver disease as an alternative to a liver transplant. While the notion of an off-the-shelf product is transformative and exciting, the potential risk for rejection, inadequate implantation and tumorigenesis raise serious concerns regarding the feasibility and success of the project. ● The stages of this project are all straightforward and logical. In general a fallback is that because the applicants are testing many lines, there is optimism that one works out. ● The applicants should further consider safety evaluations, in particular the potential for tumorigenesis. ● The applicants propose two preclinical mouse models, neither of which translate to human end stage liver disease. ● There is little mention of the impacts of liver metabolism and translation to human end stage disease.
No: 3	● The lack of a potency assay is a weakness, since end-stage liver invokes multiple liver functional deficits.It was unclear what specific defects the applicant proposes to tackle with their candidate. For example, there is no mention of how this candidate product will manage ammonium and bilirubin metabolism. ● The transplant strategy raises concerns, as end-stage liver typically comes with extreme cirrhotic conditions and it is very unlikely that this product can be delivered thru a portal vein due to the issues of life-threatening portal hypotension. In addition, the proposed therapeutic models do not represent end-stage liver disease conditions, and the translatability of the disease-modifying effect is unclear. ● The animal model does not reflect the stated target indication of the proposal. ● One concern is that fibrosis, which is common in end stage liver disease, may limit use of the proposed transplant site. ● Many of the proposed safety assays (particularly in vivo tumorigenicity assay) should be carried out after establishing pre-GMP level protocols. Otherwise, this would duplicate the team's efforts, cost, and time.
GWG Votes	**Is the project feasible?**
Yes: 13	● The proposed milestones and expected project outcome are logical and likely to be achieved within the proposed timeline of 3 years. The overall strategy, methodology, and analyses are well-reasoned and appropriate to accomplish the aims of the project. That said, concerns remain as to the off-the-shelf nature of the organoids and their ability to randomly deliver and engraft in a diseased liver, and one that is end-stage and fibrotic. This lab is well-suited to address the challenges. ● The proposed team appears to be appropriately qualified and staffed. That said, while the PI is an MD/PhD and directs a basic science lab focused on liver tissue engineering, it is somewhat surprising that the PI does not list co-investigators or collaborators on the project. Additional personnel are still to be named, including a senior research specialist, staff research associate and post-doctoral scholar to carry out the proposed studies. Together, the team appears well-suited to accomplish the stated goals. ● The current proposed plans and milestones themselves are feasible. The team is a great mix of clinicians and scientists, vital in moving complex cell therapy forward.
No: 2	● Some of the proposed culture assays may present challenges. ● The applicant should further discuss and address potential issues with CMC and GMP processes and scale up. ● The feasibility is limited by transplantation challenges. End stage liver disease may impact portal vein access, so this might not be an option for clinical scenarios. ● Alternatively, the applicants could transplant the organoids into the perineum and in other areas within the body, essentially creating mini livers.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 15	● The project plan and design adequately address and account for the influence of race, ethnicity, sex and gender diversity. In part, this is based on the fact that the PSC-derived

	liver organoids are manufactured with off-the-shelf availability and engineered to play a pivotal role in dispelling the inequities in end-stage liver disease treatment that currently depend on organ transplantation. This is a potentially ideal solution to dealing with the shortage of livers for transplantation. • In this proposed research, the PI intends to develop PSC-derived liver organoids as an abundant source of allogeneic "off-the-shelf" functional liver tissue that can be used in implantation therapy to treat end-stage liver failure. Creating a large source of PSC-based therapeutic products would alleviate much of the pressures exerted by the limited availability of life-saving tissue and the societal inequities in transplant donation and organ allocation. • Plans to address DEI are well described, with a particular focus on HLA typing for iPSC lines. • Yes, since different lines may be needed for males or females both sexes are tested, and HLA complexes most likely to be broadly accepted will be tested. • Yes, DEI principles were well incorporated. The HLA analysis to provide more equitable access across populations is one example.
No: 0	*none*

Application #	DISC2-14902
Title (as written by the applicant)	In vivo engineering of immune cells for cancer therapy
Research Objective (as written by the applicant)	These studies will advance our ability to use targeted gene therapy approaches to engineer or reprogram patients endogenous immune cells to target refractory cancer.
Impact (as written by the applicant)	These studies will enable a better, cheaper and more accessible approach for treatment of hepatocellular cancer, ovarian cancer and potentially other refractory malignancies.
Major Proposed Activities (as written by the applicant)	• Utilize targeted lentiviral vectors to express CARs in T cells, NK cells and macrophages in vitro and test anti-tumor activity. • Utilize mRNA containing lipid nanoparticles to express CARs in T cells, NK cells and macrophages in vitro and test anti-tumor activity. • Utilize targeted virus-like particles vectors to express CARs in T cells, NK cells and macrophages in vitro and test anti-tumor activity. • Direct in vivo engineering of immune cells to test for anti-cancer activity using immune competent mouse models and murine tumor cells. • Direct in vivo engineering of immune cells to test for anti-cancer activity using humanized immunodeficient mice with human immune cells and human tumor cells.
Statement of Benefit to California (as written by the applicant)	These studies aim to develop a novel gene therapy approach to better treat ovarian cancer and hepatocellular carcinoma- malignancies with few good treatment options. This approach will potentially be more accessible, cheaper and more effective than current regimens. Therefore, these studies can reduce the cancer burden for California residents. Also, since these malignancies disproportionately impact medically underserved populations, advances for these patients will be especially valuable.
Funds Requested	$2,361,860
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	76
Median	80
Standard Deviation	10
Highest	85
Lowest	50
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	2
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 14	• The proposed technology may result in a candidate to treat ovarian and liver tumors through delivery of viral vectors or nanoparticles for conversion of endogenous innate immune cells into CAR-expressing cells. • To solve these challenges associated with ex-vivo manufacturing of CAR products, the applicants propose to develop an approach for in vivo engineering of immune effector cells for CAR-redirected therapy of solid tumors. It is indeed plausible that in vivo CAR delivery would be cost-effective and might also be less immunogenic than allogeneic cell products. ◦ However, there is no rationale provided to explain how in vivo CAR delivery to T, NK, or/and macrophages would make such endogenously produced CAR cells more effective against solid tumors than ex-vivo generated CAR products. • The applicants correctly state that in contrast to CAR-T cell products for some forms of hematologic malignancies, CAR-T cells have been less successful in the treatment of solid tumors. They further argue that the current manufacturing process for autologous CAR-T cell products is too long and expensive. • Even with recent advances with the use of allogeneic cell products and/or innate effector cells as CAR carriers, ex-vivo generated CAR cell products remain cumbersome and expensive. • The applicants aim to perform in vivo transduction of immune cells with CARs/cytokines using various delivery approaches. It is an engineering approach to overcome limitations of autologous ex vivo-manufactured CAR T cells. • The unmet clinical need is there for ovarian cancer and hepatocellular carcinoma (HCC), but the likelihood of this approach being a major leap forward in these cancers is slim. The rationale for selecting these cancers seems to be towards local delivery with intrahepatic or intraperitoneal injections, respectively. • Due to a large number of proposed directions and the lack of focus, there is low probability that the results will inform successful development of a genetic therapy of clinical relevance. • Overall the application is early stage for the DISC2 program. • The applicants do not sufficiently consider translational aspects. • This is a strong proposal with no major concerns with the exception of not showing enough in vivo data.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• In vivo gene delivery is a very promising direction in general. However, scientific premise for this proposal is misplaced. Ex-vivo manufactured CAR cell products have demonstrated limited success in patients with solid tumors in large part due to factors associated with tumor biology (e.g. suppressive TME, heterogenous antigen expression, genetic instability, etc.). It is not clear how the proposed in vivo generation of essentially the same CAR cells overcomes tumor resistance. • The project is scientifically sound but a bit unfocused. There appears to be a lack of focus on which modality may demonstrate the best activity because no in vivo work has been performed in preliminary data. A severe liability of this proposal is that one or multiple of the modalities may not work in models, limiting the success of the proposal. • The in vitro preliminary data are supportive of the proposed project, but in vivo data demonstrating the development of anti-tumor immunity through injection of one of these modalities would be preferred. • The bulk of preliminary data relate to ex-vivo manufactured CAR products. There is no supportive data for a potential lead in-vivo delivery candidate.

	• A rationale for why NK and/or macrophage cell transduction would be better than T cells is lacking. • The applicants propose a systematic approach to testing different delivery vehicles with a focus on engineering NK cells and macrophages over T cells (seemingly because it has already been published that T cells can be engineered this way). However, it is not clear why engineering NK and macrophage cells will be more potent than engineering T cells. The applicant's explanation that this would be a valuable use of lineage-specific signaling domains in CARs makes it more interesting, especially given the PI's background in NK cells. • The fact that the applicant's lineange-specific CAR for NK cells works and improves NK cell activity and is now in translation as an iPSC-derived CAR-NK makes the selection of these CARs more compelling. Transduction of macrophages is likely to lead to antigen presentation, but it is not clear that this makes the transduced cell a good effector or killer. • The data in Figure 2 were generated with different kinds of cell lines (different lineages), but it would be better to look at primary cells since these are easily available to test lenti- or virus like particles. The use of antibody mimetics for specificity of transduction is novel, and comparison to alternative antibody configurations is rigorous. • There are good preliminary data to support the molecules that the applicants are planning to transduce.
No: 1	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 12	• The project design is excellent. The applicants present a very systematic and rigorous approach combining and comparing delivery and targeting approaches. • The project is well-constructed, and there is a systematic project rationale for targets. The use of in vitro, immunocompromised, and immunocompetent models adds quality and rigor. • Consideration of non-specific targeting/off-target transduction is present; however, tropisms may not be enough and less attention is given to transduction efficiency and subsequent potency at scale. • Yes, the applicants spend considerable effort and discussion on pitfalls, tranduction failures, and off cell target risks. • The project plan is too diffuse.

No:
2
	• The project proposes too many directions and is largely unfocused.
	• The plan is unfocused. The applicant could focus the application with prior identification of the best modality for further evaluation through preliminary evaluations and then focus on development of that modality.
	• There are a number of potential pitfalls identified, but these are mostly of technical nature. Significant pitfalls are not addressed such as the following:
	  ◦ Lentiviral vectors (LLV) have been shown to be safe when used for transduction of mature T or NK cells ex vivo. Despite proposed LVV targeting to T/NK/macrophages, off-target gene transduction including in stem cells is expected that may cause insertional mutagenesis and lead to transformation of stem cells and their progenies.
	  ◦ Transient expression with NPs or VLPs is expected to have short CAR expression, especially in T and NK cells that quickly divide upon target recognition. Multiple repeat treatments would be required and will likely be immunogenic with the proposed particle/vector compositions.

GWG Votes	**Is the project feasible?**
Yes: 10	• Preliminary data are light, and especially in vivo data. • The strong application is a good indicator of feasibility.
No: 4	• The PI and team are highly experienced and qualified for the project. • The project team is highly capable. • The applicants benefit from strong internal and institutional resources and track records. • The team has access to all the necessary resources. • The budget is appropriate. • The plan is well delineated and ambitious but systematic.

	• Some, but not all, milestones of the project will likely be completed within the 3-year timeline. • Overall, due to too many directions, the project is unfocused and only partly feasible. • The redesign of CAR constructs required for their use in syngeneic mouse models in aim-2A renders in vitro data generated in aim-1 using human cells largely irrelevant. • Human immune cells, especially T cells generated in hu-NSG mice are rare and dysfunctional raising concerns for feasibility of the proposed experiments in aim-2B. • Preliminary data in vivo or in mixed cultures would be helpful to demonstrate feasibility. • The lack of in vivo data challenges feasibility.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 14	• The project plan and design adequately address and account for the influence of race, ethnicity, sex and gender diversity. • The project's early state in the discovery phase makes it challenging to address DEI, but the project has the potential to serve diverse groups.
No: 0	*none*

Application #	DISC2-15048
Title (as written by the applicant)	Engineering tunable biomimetic adhesive hydrogel to deliver and enhance MSCs function for corneal regeneration.
Research Objective (as written by the applicant)	We propose a minimally-invasive adhesive MSC-laden hydrogel with tunable properties that can release MSCs in the cornea in sustained manner while mimicking its biomechanics to repair ocular injuries.
Impact (as written by the applicant)	Engineered MSC-laden adhesive hydrogels can enhance MSC survival and retention, control release and dosage, support cell ingrowth, facilitate tissue regeneration, and seal and repair stromal injuries.
Major Proposed Activities (as written by the applicant)	• Aim 1. Engineer MSC-laden adhesive hydrogels based on modified gelatin and hyaluronic acid with tunable physical properties • 1.1. Synthesis of a soft adhesive hydrogel for promoting epithelial growth, • 1.2. Synthesis of a strong adhesive hydrogel for the repair of stromal injuries • Aim 2. In vitro characterization of the engineered MSC-laden adhesive hydrogels • 2.1. Assess MSCs survival and secretion of factors within the soft hydrogel and its effects on epithelial growth under the hydrogel in vitro • 2.2. Study in vitro migration of MSCs from the strong hydrogel as well as epithelial growth on top of the hydrogel • Aim 3. In vivo characterization of the engineered MSC-laden adhesive hydrogels in a corneal epithelial wound model and stromal injury model
Statement of Benefit to California (as written by the applicant)	The proposed research addresses the high rate of ocular injuries in California (~52,000 emergency department visits) by developing an alternative treatment using mesenchymal stem cell (MSC) therapy. By addressing issues of tissue donor shortage and invasive surgical methods, this new therapy will broaden treatment options for patients and promote health equity in California. The incorporation of diversity, equity and inclusion (DEI) concepts further ensures that the therapy benefits all patients, regardless of their background or socioeconomic status.
Funds Requested	$1,998,474
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	76
Median	80
Standard Deviation	7
Highest	84
Lowest	62
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 15	• The proposed technology consists of a combination of mesenchymal stromal cell (MSC) and cornea adhesive hydrogel to promote healing and regeneration of corneal epithelial and stromal wounds. This could impact an unmet medical need. • An effective MSC therapy could provide a new treatment option for patients who do not respond well to current treatments. • MSC delivery to the cornea has shown beneficial effects. Poor MSC survival to date has been potentially due to use of non-ideal biomaterials. • This is a large unmet need.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 11	• The rationale for using MSC to repair the cornea is sound. However, the cell sourcing, assays and identification are not well delineated in the proposal. How are the MSCs identified and described? MSCs can be very heterogeneous. • The rationale for use of some specific biomaterials could be better discussed and explained - i.e., using comparisons with other polymers. How will the gel be optimized? • A risk that is not discussed is the potential degradation of polymer by the ocular surface environment, which includes hyaluronidase, gelatinases, and cytokines.
No: 4	• The biomaterial part of the proposed project is based on a sound scientific rationale. It has been demonstrated that hydrogels can be designed to exhibit specific mechanical and tissue adhesive properties. Also, hydrogels can be formulated to support cell survival, proliferation, and differentiation. • The scientific rationale for the MSC part of the project is less sound. There have been reports of significant adverse effects of MSC injection into the eye. Also, conclusive reports of MSCs' therapeutic efficacy in the eye are still lacking, and the proposed project does not include a detailed investigation of the biological effects of MSCs in their system. • Although the applicant states that the project will include establishment of the identity and purity of the MSCs, no experiments are proposed to this effect. • There are some concerns on the safety of MSCs in the eye and the lack of cell characterization in the proposal. • The rationale for using the proposed biomaterial is weak. The preliminary data do not provide a strong rationale for the combination product of MSCs plus combination hydrogel since they were generated with different hydrogel formulation and/or cell types; the claimed increased survival of MSCs after delivery to the cornea using the proposed hydrogel system is not supported. • Preliminary in vivo data lack controls using other types of biomaterials and/or bioadhesives.
GWG Votes	**Is the project well planned and designed?**
Yes: 12	• A strength is using the same base hydrogel for the two hydrogel products. • Another strength is the hydrogel optimization in Aim 1 - the use of definitive screening design (DSD) to optimize the two hydrogels and reduce the complexity based on multiple parameters. • There are concerns about the biological aspects of the project (which seem underdeveloped) and lack of a plan for managing collaboration. • Details of cell sourcing for the clinical product are missing. • Alternative strategies for Aims 2 and 3 will require re-optimizing the hydrogel design of Aim 1. • More details are needed on the communication and collaboration plans. • MSCs are not adequately characterized in the project plan.

No: 3	• The design for bioengineering the adhesive hydrogels is appropriate, and these efforts are likely to achieve the expected outcome. • However, proof-of-principle experiments to demonstrate the translational promise of the hydrogel-MSC are not well-developed.
GWG Votes	**Is the project feasible?**
Yes: 14	• This is a multidisciplinary project over three years with clearly defined tasks for each team member and quantifiable success criteria. • This has a high likelihood of success. The risks are in the fine tuning of the polymers and in the safety of MSCs on the ocular surface.
No: 1	• The milestones are logical but the project's outcomes, especially Aim 3, are not likely to be achieved within the proposed timeline. • Overall, the team is appropriately qualified. However, the collaborating teams are not local to each other, and no specific plans are presented for how the effort of the three teams will be integrated.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 15	• By overcoming a need for corneal donor tissue (which is in short supply) and the requirement for surgical intervention for treatment of corneal injuries, the project, if successful, will increase accessibility for the patient populations of different race and ethnic origins. • The MSC cell lines will be collected from donors with diverse backgrounds, ethnicity, sex, and race. • The proposal includes appropriate discussion of DEI. • Overall, the DEI section could be more robust.
No: 0	*none*

Application #	DISC2-15147
Title (as written by the applicant)	Treating Limbal Stem Cell Deficiency with Induced Pluripotent Stem Cells
Research Objective (as written by the applicant)	Our aim is to create limbal progenitor cells differentiated from patient-derived induced pluripotent stem cells in order to cure blindness by regenerating limbal stem cell deficiency (LCSD) patients' ocular surface.
Impact (as written by the applicant)	There are no durable treatments for bilateral limbal epithelial stem cell deficiency patients. Autologous iPSC based limbal stem cell replacement would revolutionize therapy and restore vision.
Major Proposed Activities (as written by the applicant)	• TMEM158+ or SLC6A6+ human and mouse limbal cell isolation and analysis • Human and mouse limbal niche dissection with spatial transcriptomic and CytoSPACE analyses • TMEM158+ or SLC6A6+ cell grafting • iPSC TMEM158 or SLC6A6 gene modulation and differentiation assessment • How TMEM158 or SLC6A6 modulates LSC graft self-renewal and differentiation in LSCD mouse and rabbit models
Statement of Benefit to California (as written by the applicant)	Limbal stem cell deficiency is a leading cause of untreatable corneal blindness among the almost 40 million Californians. Our research to create transplantable autologous limbal progenitor cells would allow treated patients to return to school and work, no longer afflicted by this painful, blinding disease. In addition to the health care and social services savings this cure would bring, considerable investment in these technologies would attract jobs and other revenue to our state.
Funds Requested	$2,311,200
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: 78

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

Mean	76
Median	78
Standard Deviation	3
Highest	80
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 13	• This project aims to address limbic stem cell deficiency, which most often occurs through trauma (burns) and as a consequence of other diseases. The limbic stem cells replenish the corneal epithelium. These cells can sometimes be transplanted as autologous from one eye to the other, but that doesn't work when both eyes are damaged. The investigators propose to develop iPS-derived limbic stem cells that could be used in these instances. • For bilateral LSCD there is tremendous unmet need. • The bottlenecks so far have been around defining markers for limbic stem cells to induce their differentiation and make sure that they retain stem cell properties. The investigators have discovered two new markers of limbic stem cells which are related to a signaling pathway and ion transport.
No: 2	• This is a solid application from a well established group of collaborators. However, the project is too early stage to be an appropriate fit for the DISC2 mechanism. The project is still at a very basic science stage, and would benefit from further development to define potential lead candidates for selection. It is also unclear how much of a significant advance these gene markers may represent in terms of a therapy for clinical translation. • The project is too exploratory to meet the expected outcome of the DISC2 program.
GWG Votes	**Is the rationale sound?**
Yes: 13	• The rationale is that by validating new LSC associated genes, it would be possible to enrich for LSC populations and then further specify the LSC marker signature, thus enabling more effective LSCD therapies. This study will help to identify new genes that can modulate and improve iPSC likelihood for success for LSC therapies. • This is a very well written proposal that includes very exciting use of iPS-derived cells for a clinically significant problem. Although it is not clear how many people are affected, the proof of concept is very strong. • The rationale for the project is sound. • The preliminary data are highly supportive of their plan and are well presented. • The rationale is sound, but the project is at a very early stage. It is not clear that the two genes identified would support better enrichment of LSCs. • The application needs more preclinical data and justification that it is indeed these two genes that should be upregulated to improve limbal stem cell function and survival. • It is unclear how the applicants will harvest cells for eventual clinical use. Will the cells be from human donor corneas?
No: 2	• There are not enough preliminary data to support undertaking this work on the basis of the proposed two genes.
GWG Votes	**Is the project well planned and designed?**
Yes: 9	• The project is well planned and thoroughly described.
No: 6	• The experimental plan is rigorous and systematic. Multiple models are used; expected outcomes and pitfalls are thoroughly explored. • This project may be too premature for the DISC2 mechanism because the path to clinical translation is a bit murky. Consideration is given to potential safety, re-differentiation issues, and immunogenicity, for example, but these studies are not included in the experimental plan. In addition, the experimental plan is designed to address the mechanisms and role of these two new markers in defining limbic stem cells and their functional role in differentiating to corneal epithelium. • It is unclear if the two genes identified are actually genes that improve iPSC survival and engraftment. • The animal models are not adequately described. It is unclear what the endpoints, timelines, statistical analysis/power, and comparisons/controls will be. • The study is designed to explore gene function and not to generate a candidate ready for translation.
GWG Votes	**Is the project feasible?**
Yes: 14	• The proposed milestones are logical and likely to be achieved in the proposed timeline.

	• The proposed team is appropriately qualified and staffed, and they have access to necessary resources to conduct the project. • The group is well-equipped to carry out the proposed research. • The budget is appropriate for the proposed research. • The project is feasible but more clarity is needed around the target product.
No: 1	*none*
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 15	• The plan to incorporate DEI and address DEI issues is reasonable; the disorder appears to be relatively rare and there are little data on health disparities but these are likely related to overall access to care. The applicant's plan to involve patient groups will address this, including in underserved areas. • The project outcomes will inform the development of a product or tool that serves the unmet medical needs of the diverse California population, including underserved racial/ethnic communities. • Principles of DEI are adequately addressed.
No: 0	*none*

Application #	DISC2-15070
Title (as written by the applicant)	Development of next-generation human cerebellar organoids to model hereditary cerebellar ataxias
Research Objective (as written by the applicant)	Next-generation cerebellar organoids will allow robust recapitulation of human cerebellar development and degeneration leading to the identification of effective treatments for cerebellar ataxias.
Impact (as written by the applicant)	Next-generation cerebellar organoids will solve a bottleneck in the field by providing for the first time reliable and consistent recapitulation of human cerebellar dysfunction and degeneration.
Major Proposed Activities (as written by the applicant)	• Generation of long-term culture of organoids that reproducibly form cell diversity of the human cerebellum. • Testing of reliable and consistent recapitulation of cerebellar neuronal dysfunction and degeneration in human cerebellar organoids derived from SCA36 patient iPSCs
Statement of Benefit to California (as written by the applicant)	In addition to improving the understanding and screening of drugs for hereditary cerebellar ataxias, our model will be a valuable resource for the broader biomedical community interested in modeling dysfunctions in other types of human brain disorders with cerebellar involvement including complex mental disorders and cerebellar cancers, by delivering the first high-throughput platform for effective drug screening in distinct types of human cerebellar cells.
Funds Requested	$838,710
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: 77

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	77
Median	77
Standard Deviation	2
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 project hold the necessary significance and potential for impact?
Yes: 13	• Yes. Animal models are of limited use for this disease, and the proposed human organoid model offers a unique and exciting new opportunity to address disease pathology. • The applicants will develop an organoid model for screening therapeutics for cerebellar diseases, which addresses an unmet need. • The proposed model could be used beyond this rare cerebellar disease. • The proposal targets a significant disease and has wider applications. • The proposal addresses cerebellar ataxias, rare diseases with devastating consequences and no treatment. Robust cerebellar organoid technology would find application in many central nervous system diseases. • A drug screen using the model is included in the proposal.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• Cerebral ataxias are a major disease challenge and animal models have shown limited success in recapitulating these disorders. No effective approaches to halt or prevent the disease have been identified. This project addresses a significant unmet medical need. • The applicant recognizes and attempts to address the importance of cellular maturation for disease phenotyping. Organoid (versus 2D culture) should enhance maturation of cerebellar neurons due to the more complex and instructive microenvironment in an organoid. • The proposal includes good preliminary data on cerebellar organoids. Patterning with morphogens reduces the percentage of off-target cell types in the model. • The rationale is sound. It will be useful to build a new organoid drug screening model. • The rationale for disease modeling in organoids is sound. • Overall, yes, though preliminary data are somewhat weak.
No: 2	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 11	• Overall yes, but there are a number of concerns. Based on previous critiques, the applicant now provides a single cell RNA sequencing analysis of patient-derived organoids compared to normal healthy organoids. They provide preliminary data showing increased mitochondrial stress-related transcription in the patient-derived organoids. • The preliminary data confirm that (i) patient derived organoids can indeed be generated in a reproducible manner, (ii) that these organoids contain all the required cell populations that are expected to define cerebellar fates, and (iii) the patients' transcriptional profile is different. • Unfortunately, their may not be a cellular phenotype that defines the patient-derived organoids or could serve as an endpoint for drug screening (proposed in Aim 3). While the applicant speculates that neuronal cell death may happen in a disease-specific manner, no data are provided to support this hypothesis. • Plans for quantification of dendritic arborization are not clear. The applicant shows one neuron in two-month organoids at a high magnification, making it difficult to see how potentially complex arbors in older organoids could be quantified. It is also not clear whether a dendritic arborization readout will register a difference in patient versus normal organoids. • Overall, yes, but the applicant should consider the impact of hypoxia on this organoid model. • The project plan for the small molecule screen is not sufficiently detailed for evaluation.
No: 3	• The applicants have not adequately developed cerebellar organoids with a measurable phenotype. • More detail on therapeutic screening is needed, as well as more detail on the pathology in organoids. • The issue of planning drug screening came up at the last review. This has been addressed somewhat but only with the statement 'small molecule screen' and the inclusion of a team member with expertise in this area.

	• While the proposal to enhance the maturation of organoids is sound, the disease modeling aspect is still weak, with no convincing phenotype that would be amenable to readout in screening assays. It's disappointing that the applicants cannot provide a stronger response here. • The disease phenotype is still not well characterized; the screen cannot proceed without this key parameter of the model. • The plan to introduce repeat expansions with adeno-associated virus (AAV) is poorly articulated, and it's not clear precisely what the authors are doing here. • Using AAV to mark neurons for use in screening assay endpoints may be subject to variability, thereby increasing noise in the assay. • Further maturation of the organoid may increase variability. Larger organoids may lead to problems with hypoxia and lack of nutrition. • It's not clear that the proof of concept experiments will be completed within the necessary timeframe.
GWG Votes	**Is the project feasible?**
Yes: 11	• While the applicant proposes a small molecule screen to ameliorate pathological features in their model, which would allow for rapid translation into clinical use, no specific plan is laid out. • Cell death as an outcome is problematic and might normally occur with time. It will, therefore, be difficult to determine what levels of cell death are disease-specific. • The applicant proposes to use AAV to introduce the (TG3C2)62 repeat expansion mutation into cerebellar organoids generated with iPSC lines from three healthy donors with different ethnicities, but no preliminary data are provided to show feasibility. • No mitochondrial-specific assays are proposed, despite the preliminary data that suggest mitochondrial dysfunction. • Integration of the preliminary data that show differentially expressed genes in patient-derived organoids is poor, and the knowledge generated from these data is not really used to define cellular endpoints.
No: 3	• The applicant did not adequately address some key requests from the prior review, including the issue of mitochondrial dysfunction. • Without a disease organoid, the project can't move forward. • Details on the small molecule screen to be used are still lacking.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 14	• The applicant proposes to generate new iPSC lines from donors with various backgrounds and will thus address the influence of these factors on organoid generation and outcome. • The applicant will study iPSC lines from multiple races/ethnicities (Hispanic, Asian and Black) and both sexes. Presumably white, non-hispanic patients won't be included? • The project will incorporate cell lines derived from patients with diverse genetic ancestry. • The institution has a strong DEI program and the PI is thoroughly engaged in it. The PI has also been involved in CIRM's Bridges program.
No: 0	*none*

Application #	DISC2-15155
Title (as written by the applicant)	Self-delivery of a tissue-targeting CRISPR-Cas9 protein-based therapeutic for the treatment of kidney disease
Research Objective (as written by the applicant)	A tissue-specific gene-editing therapeutic will be developed to treat a kidney disease. The therapeutic platform can be applied to unmet medical needs across a multitude of tissue and cell types.
Impact (as written by the applicant)	In this disease, a toxic gain-of-function protein damages kidney cells, resulting in a rapid progression to end-stage kidney disease. It only affects people with African ancestry; no treatment exists.
Major Proposed Activities (as written by the applicant)	• Selecting engineered ribonucleoprotein (RNP) constructs • Demonstrate selective uptake of RNP constructs into kidney cells • Demonstrate on-target editing of RNP constructs within podocytes • Demonstrate amelioration of disease phenotypes in a human cellular model • Demonstrate target knockdown, biodistribution and safety in wild-type mice • Demonstrate disease modification and on-target editing in a murine disease model
Statement of Benefit to California (as written by the applicant)	It is estimated that ~12,000 African Americans have this condition in the State of California, many in dialysis and in need of a kidney transplant. While diagnosis is straightforward, there are no current approved treatments. A novel therapeutic that could prevent the onset of end stage kidney disease would have significant quality of life and mental health improvements for these patients, and have a dramatic impact on healthcare costs in CA.
Funds Requested	$1,994,848
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 75

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

Mean	76
Median	75
Standard Deviation	2
Highest	80
Lowest	70
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 12	• The proposed technology could conceivably result in a candidate that impacts an unmet medical need affecting individuals of African descent. • The project focuses on utilizing CRISPR-Cas9 technology to selectively inactivate APOL1 in the kidney, reducing the production of toxic gain-of-function APOL1 protein that drives progressive kidney disease. By targeting a clinically validated target for AMKD, the project could significantly accelerate the development of genetic therapy for kidney diseases • There are presently about 100,000 APOL1-mediated kidney disease (AMKD) known patients in the U.S. and probably many more undiagnosed. Patients carrying the APOL1 risk variant progress to end stage kidney disease within 5 years, requiring dialysis and ultimately kidney transplantation. There are currently no approved drugs that address the underlying cause of AMKD. As such, it is a highly unmet medical need. • With no current approved drugs addressing the underlying cause of AMKD, the project aims to fill a highly unmet medical need, particularly in the treatment of APOL1-mediated focal segmental glomerulosclerosis (FSGS). • This is a very attractive target for gene deletion as APOL1 is not required but the presence of the APOL1-G2 variant results in FSGS. There is considerable significance of this in the African American community. The advantage of a single gene editing procedure over a long term drug is advantageous. • Kidney disease is an unmet need.
No: 2	*none*
GWG Votes	**Is the rationale sound?**
Yes: 6	• The project leverages CRISPR-Cas9 technology, a well-established method for genome editing, to selectively target APOL1 in the kidney. The rationale is grounded in the understanding of APOL1-mediated kidney disease and the need for targeted therapy. The project builds on existing knowledge and aims to develop a therapeutic approach that addresses the underlying cause of AMKD. • The application lacks compelling in vivo preliminary data on podocyte targeting and uptake via the proposed receptor. • It is concerning that the Cas9 fusion protein and sgRNA may not be able to pass the endothelium.
No: 8	• The proposed project is based on scientific rationale that includes (i) engineering a diverse set of RNPs optimized for APOL1 modified sgRNA serum stability, endosomal escape, nuclear localization, and optimal targeting to human kidney podocytes; (ii) confirmation of reduced levels of the toxic APOL1 in diseased human kidney cells; and (ii) mechanism(s) of action, biodistribution, and safety in a valid clinically relevant APOL1 transgenic mouse model. • There is a lack of preliminary data for several of the milestones, including podocyte targeting and uptake via the proposed receptor, which is presumably highly expressed in those kidney cells. Additional preliminary data would have been supportive for the proposed milestone to generate a transgenic APOL1 mouse model homozygous for the APOL1 G2 variant. • While the approach is state of the art, the approach to targeted delivery into podocytes is problematic as the evidence that the proposed target protein is a specific ligand for entry into podocytes is lacking. The applicants suggest an alternative ligand, but this choice is not feasible as this is a transmembrane protein that forms a critical component of the slit diaphragm. It is not a receptor binding ligand. • Kidney targeting via the proposed receptor is not rationalized. • The use of RNPs, instead of lipid-based nanoparticles for delivery, is not adequately justified. • The applicants should further consider challenges in culturing podocytes, and whether these are the right cells to target for this disease.
GWG Votes	**Is the project well planned and designed?**
Yes: 10	• The project is appropriately planned and designed to achieve the expected outcomes, including proof-of-concept data for a product candidate that is ready to advance to translational studies. That said, critical to the success of the project is efficient podocyte targeting, editing and generation of a ALOP1 G2 transgenic mouse model. The product

	therapeutic could potentially be used for the treatment of a wide variety of monogenic disorders. • This is a well-constructed, quality project with some risk. The experimental design is logical and supported by preliminary data but primarily only for milestone 1. Potential pitfalls and alternative approaches are considered, and the research plan would suggest that the project could possibly be completed within the timeline of 18 months. That said, it will require successful targeting to the proposed podocyte receptor, and the development of a new transgenic mouse for the APOL1 G2 variant of disease within this time frame. • This is a well designed program, but a very ambitious one. However, the team have considerable experience with the use of modified Cas9 proteins and RNPs and if proof of concept is achieved with respect to selective and tissue targeted gene deletion, this would rapidly more through to clinical trial. However, the timeline is possibly too short to achieve all stated outcomes, particularly the animal modeling. • The project appears well-constructed, focusing on a significant unmet medical need and leveraging innovative CRISPR-Cas9 technology.
No: 4	• The project is very ambitious and the argument supporting the proposed podocyte targeting approach should be strengthened. • The rationale provided for the proposed podocyte target suggests that additional podocyte biology expert could be beneficial to the team.
GWG Votes	**Is the project feasible?**
Yes: 6	• The team appears to be appropriately skilled with the exception of any evidence of experience with the kidney and podocyte culture approaches. • This project may not be feasible within the proposed time frame. • The proposed budget seems excessive for the planned activities.
No: 8	• The PI and their team appear to be well suited to the project. They provide complementary and integrated expertise to the study; and at least two TBD scientists and a research associate are included in the list of personnel. In addition, intellectual support from a well regarded academic founder is a major advantage for the team. • The proposed milestones and project outcome are logical, with concerns that it will be difficult to achieve milestones 5-6 within the timeline of 18 months. This is based on preliminary data that is lacking to support those milestones, the feasibility of targeting the product to podocytes within the complex structure of the glomerulus, and the development of an ALOP1 G2 mouse model that is accurate to the human condition. The overall strategy is well-reasoned and appropriate to the project. • The ligand may not be the ideal ligand. It is kidney specific, but not a key ligand and not specific for podocytes. • The proposed product has low feasibility of efficiently targeting the glomeruli. • The budget is excessive for the studies that are described over the timeline of 18 months. In addition, the preliminary data would suggest that some of the milestones have either been achieved or are very close to being achieved. • Two major feasibility issues are the specificity of the ligand selected for kidney targeting and the generation of the humanized transgenic APOL1-G2 mouse strain. • The need to make a new mouse model drives concerns about the timeline.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 14	• Overall, yes, the project plan and design address and account for race, ethnicity, sex and gender diversity. ALOP1 disproportionately affects individuals of African ancestry. Individuals involved with the applicant organization are fully committed to DEI at their host academic institutions. The applicant organization is committed to making the therapeutic available and accessible to all underserved patients, and particularly those of African descent. • The project outcomes would develop a product that would serve the unmet medical needs of the diverse population of CA, including underserved racial/ethnic communities. This is clearly stated in parts 2 and 3 of the DEI section of the proposal. Success will require a strong relationship with patient advocacy groups, the American Kidney Foundation, and a wide variety of under represented Black communities. The intended product is designed to work across races, ethnicities, gender, and age. • APOL1-G2 associated AMKD is specifically elevated in the African American population. This condition is currently untreatable, although there is a drug in Phase 3 clinical trial at

	present. The applicants appear to be aware of the need to work with patient advocacy groups although this appears not to have commenced at this point in time. • The project recognizes that AMKD disproportionately impacts individuals of African ancestry and emphasizes the need to address this specific population. The proposal includes considerations for diversity, equity, and inclusion in both the overview and product development • The applicant emphasizes the need to work with patient advocates, clinicians, and hospitals to advance education and improve diagnosis and treatment. They recognize the importance of community engagement but do not detail how perspectives and experiences from the population will be incorporated.
No: 0	*none*

Application #	DISC2-15145
Title (as written by the applicant)	A small molecule therapeutic to differentiate cancer stem cells
Research Objective (as written by the applicant)	We will develop a small molecule that blocks the growth of human triple negative breast cancer stem cells in vitro and in vivo.
Impact (as written by the applicant)	This work will lead to a new treatment for cancer stem cell driven triple negative breast cancer, and it will improve patient prognosis.
Major Proposed Activities (as written by the applicant)	• Target and mechanism of action identification of two small molecule leads • Multi-dimensional hit-to-lead optimization of small molecule candidate to increase cancer stem cell-differentiation activity and in vitro absorption, distribution, metabolism, excretion and toxicology. • In depth in vivo drug metabolism and pharmacokinetics studies with best performing lead series • Measure and model pharmacodynamics in patient-derived organoid models • Demonstrate efficacy of lead compound alone and in combination with chemotherapy in patient-derived xenograft models of triple negative breast cancer
Statement of Benefit to California (as written by the applicant)	Triple negative breast cancer is prevalent in the State of California. Because this research will lead to development of new treatments for this diseases, the citizens of California will directly benefit. Triple negative breast cancer affects people of all ethnicities and socio-economic status. Thus, if successful, the new therapeutic will improve outcomes for patients throughout the State of California.
Funds Requested	$2,376,000
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: 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	73
Median	75
Standard Deviation	3
Highest	79
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 14	• The project aims to develop a small molecule that targets triple-negative breast cancer (TNBC), which represents a major unmet medical need. • The proposed small molecule candidate has an unusual mode of action through the induction of differentiation in cancer stem cells (CSCs), making them more sensitive to standard chemotherapy drugs. Therefore, the new drug may synergize with the existing therapy, overcoming drug resistance, a major feature of TNBC. • There is a well-presented path for progression from testing the candidate and its analogues using in vitro screens, in vivo testing, and further IND-enabling studies of the lead candidate. There is also a plan for the inclusion of the new drug in the current treatment strategy for TNBC patients. • Cancer stem cells are thought to be an important contributor to the resistance of cancers to various types of treatment. The ability to differentiate cancer stem cells into cells that either do not replicate or are more vulnerable to chemotherapy and radiation would be highly impactful.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• There is a strong rationale for further testing of the small molecule lead and its analogues based on robust preliminary data in TNBC cells grown in 3D culture. The data shows that the lead molecule induces CSC differentiation and sensitivity to doxorubicin in TNBC cell lines and patient-derived organoids. • There is evidence that the lead molecule selectively targets CSCs, not normal stem cells, through the activation of the Notch pathway. Another consideration for safety comes from a prior study, which found that treatment with the lead molecule was safe in mice. • This is a revised, resubmitted application that has made significant improvements, and it has a sound rationale. • At least an initial signal of antitumor activity in vivo would be important for establishing a proof-of-concept. • Theoretically yes, but preliminary data are not convincing.
No: 3	• The rationale for drug development is strong. • The biological aspects of the work are weaker. For example, the experiments shown in Figure 6 show that the response to treatment with the lead molecule is very heterogeneous. This is not discussed, which is a big problem because eliminating 25% of CSCs may not matter.
GWG Votes	**Is the project well planned and designed?**
Yes: 5	• The experiments are well planned, with appropriate controls and statistical considerations. There is a clear in vitro activity for the lead molecule and one of its analogues against CSCs. The results justify further testing of the candidates in a series of translational studies as proposed. • There is attention to potential pitfalls and description of alternative approaches. In particular, the applicant would produce and screen an extended library of lead analogues that will likely increase the likelihood of success. • In addition to typical therapeutic development experiments, the project is also very mechanistic. The potential discovery of new molecular targets in breast cancer CSCs further increases enthusiasm for this project. • However, there is still a significant risk that the drug may not be active in a mouse tumor model.
No: 10	• No in vivo activity studies are planned in the early stages of the project, which makes it challenging to make a quick go/no-go decision on whether to proceed. • Despite the in vivo use of the lead molecule by others, there are no in vivo tests of the applicant's core hypotheses of improved cancer treatment. • There are concerns about the lack of proposed in vivo studies to demonstrate activity.

	• The proposal needs additional in vivo data. • No in vivo data are provided. • There is no simple in vitro assay for tumor spheres in vitro, and there would be a benefit in seeing and determining efficacy. • The CSC analysis is biologically unsound. Aside from the heterogeneity of response, there is no analysis of biological CSC activity. More specifically, there is no use of straightforward in vitro analyses of tumor sphere growth to test for CSC elimination in vivo. Even more critically, there are no limiting dilution transplantation experiments, which are essential for demonstrating the elimination of CSCs.
GWG Votes	**Is the project feasible?**
Yes: 12	• The proposed milestones and expected project outcome are logical and likely to be achieved within the proposed timeline, • The PI and team are well-qualified for the project. • The institutional environment for the proposed work is excellent. • The budget is appropriate. • Unfortunately, numerous design flaws make the probability of success low.
No: 3	• There is a need for in vivo model studies to show reduction of tumorigenesis with the cell-line derived model as well as decrease of tumor growth with lead molecule treatment. • Feasibility is difficult to evaluate because critical information on the efficacy of CSC elimination is not provided. Such information is essential to evaluate the merit of this approach.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 14	• The project plan and design adequately address and account for the influence of race, ethnicity, sex and gender diversity. • TNBCs, and poor outcomes, are over-represented in Black women.
No: 1	*none*

Application #	DISC2-15072
Title (as written by the applicant)	Functional chemical screens in human iPSC-derived cardiomyocytes to identify new cardioprotective drugs
Research Objective (as written by the applicant)	We aim to identify cardioprotective drugs to improve heart preservation and transplantation.
Impact (as written by the applicant)	Many donor organs are not transplanted due to inefficient preservation conditions. Our study may help prolong cold storage and increase the number of organs to be transplanted.
Major Proposed Activities (as written by the applicant)	• Chemical screen for novel cardioprotective compounds using human iPS-derived cardiomyocytes • Validation of top hits of compounds using chemicals from independent sources • Test these compounds in cardiomyocytes derived from human iPSCs of diverse ethnicity • Examine the effects of chemical compounds in primary human and mouse cardiomyocytes in vitro and mouse heart ex vivo • Examine the effects of top chemical candidates in mouse organ transplantation in vivo, and test short-term outcomes • Examine the effects of top chemical candidates in mouse organ transplantation in vivo, and test long-term outcomes
Statement of Benefit to California (as written by the applicant)	Over 23,000 Californians are currently waiting for organ transplants. This proposed research will extend organ extracorporeal lifetime, expand the number of recipients, and save the lives of many patients affected by end-stage organ failures in California and beyond.
Funds Requested	$813,000
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 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	72
Median	75
Standard Deviation	4
Highest	75
Lowest	65
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 14	• Cold storage of organs would provide many new therapeutic options. • The project is using the iPSCs as a screening method for drug development for eventual in vivo use. • The project aims to identify novel chemical compounds that protect human cardiomyocytes from hypothermia-induced cell death, prolonging heart cold storage and improving heart transplantation. This may not be the big concern in iPSC-CM transplantation. • The project focuses on the development of novel chemical compounds for organ transplantation improvement, specifically for patients with end-stage organ failure.
No: 1	• The PI intends to pursue a class of inhibitors which may have increased risk of serious heart-related events, cancer, blood clots, and death. A product that has these issues may be counterproductive.
GWG Votes	**Is the rationale sound?**
Yes: 8	• The project is based on identifying new cardioprotective chemical compounds for heart cold storage and transplantation. • The data from the applicant on generating mature hPSC-CMs is not compelling.
No: 7	• It is unclear if the iPSCs are actually representative of human myocardiocytes. • The cardiomyocytes are not well characterized; preliminary data comparing human cardiomyocytes with induced ones is missing. • The focus on cardiomyocytes is too reductionist. • Not a validated model and wrong choice of meds to study. • Project progresses from screening to in vivo testing but focuses on a class of inhibitors which can have adverse effects on the heart. • Compounds have been shown to have many severe clinical side effects raising issues about clinical feasibility. • Removal of the CRISPR focus and replacement with more in vivo testing did not strengthen the application because it is less unique; retention of this program could facilitate its cutting edge approach.
GWG Votes	**Is the project well planned and designed?**
Yes: 10	• The proposal includes the identification of new cardioprotective chemical compounds for heart cold storage and transplantation. The plan is designed to demonstrate cardioprotective activity in various models and establish feasibility for later extension to heart transplantation tests. • The application includes a more feasible completion timeline and addresses concerns about the viability threshold in the primary chemical screen and the maturity of human iPSC-derived cardiomyocytes. • Nice outcomes measures in first milestone. • It is unclear if the applicant can make mature hPSC-CMs. • No alternative approach is outlined in Aim 1.
No: 5	• Additional preliminary data is needed to confirm the feasibility of the project. • No sample size estimation, no clear dose response etc. • Cardiomyocyte differentiation is not well characterized. • Sample size and power calculations are missing. • By mixing high throughput screening with drug development feasibility studies, the feasibility studies are less robust. • Project would benefit from adding a cardiologist or toxicologist for experimental design planning.
GWG Votes	**Is the project feasible?**
Yes: 8	• The screen is feasible but the results might not be clinically appropriate. • The team may need expertise on how to make mature hPSC-CMs.
No:	• Drug development approach and design is lacking.

7	• Concerned that a lot of time and effort will be wasted on developing a class of inhibitors which in the clinic are not friendly to the heart. • The use of the proposed class of inhibitors is unclear. • No sample size, no statistics, dose response in vivo - not well thought out. • If sample size and power calculations are not disclosed, there is no way of knowing if the project is feasible. • Two months is not really long term survival in heart transplant studies in mice. • Concerns of expertise.
GWG Votes	**Does the project uphold principles of diversity, equity and inclusion (DEI)?**
Yes: 15	• This is an outstanding consideration using minority sources for cells; it presents a major strength of the proposal. • Very strong. • Differentiate iPSC from minorities to induce myocardiocytes. • The project demonstrates good-faith efforts to uphold principles of DEI by addressing and accounting for race, ethnicity, sex, gender, and age diversity in the project plan and design. • The applicant does not provide specific details on how the project outcomes would directly serve the unmet medical needs of the diverse California population, including underserved racial/ethnic communities.
No: 0	*none*

Application #	DISC2-14886
Title (as written by the applicant)	Development of spinal cord tissue using human spinal cord stem cells and 3D-printed drug-delivery scaffolds for acute spinal cord injury repair
Research Objective (as written by the applicant)	Effective functional neuronal relay through spinal cord injury using human spinal cord stem cells in 3D-printed drug-delivery scaffolds
Impact (as written by the applicant)	300,000 Americans have sustained some form of spinal cord injury (SCI), resulting in permanent disability. There are no effective therapies for SCI, representing a great unmet medical need
Major Proposed Activities (as written by the applicant)	• Optimize Scaffold Design - Methods development to 3D-printed scaffolds with drug-delivery nanoparticles • Optimize Scaffold Design - Bioactivity characterization • Test therapeutic using in vivo model of spinal cord injury
Statement of Benefit to California (as written by the applicant)	300,000 Americans have sustained spinal cord injury (SCI) with an estimated lifetime care cost for a 25-year-old, high tetraplegic patient of $4.6M. There are estimates that southern California experiences ~1,000 new cases/year. Thus, SCI directly affects the lives of Californians that were injured, their families and caregivers. A therapy for SCI would not only benefit the patients in California their families and caregivers, but it will also save many working days lost by the injury.
Funds Requested	$2,232,190
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: 74

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	74
Standard Deviation	4
Highest	85
Lowest	65
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	1
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes:	• Spinal cord injury is a tremendous unmet need.

13	• Spinal cord injuries represent a significant unmet medical need. The proposed candidate uses a cellularized scaffold containing a factor to accelerate and enable healing severed spinal cords. • The proposed approach is a promising candidate for SCI. • This study will provide preclinical rat data which would motivate studies in larger animals more relevant to human translation. • The team has a startup based on the scaffold as a spinal cord therapy. This or another company could be used to achieve translational goals.
No: 2	• This is a technologically well defined application that could provide improved biomaterials and stem cell products for repairing certain types of injuries to the central nervous system. • The problem is that the lesion system to be tested is an artificial one that does not model human SCI. Thus, even if this works perfectly it is not clear whether it would work in a human-relevant lesion.
GWG Votes	**Is the rationale sound?**
Yes: 9	• This project is well thought through, well presented, and based on sound scientific rationale and preliminary data. Presented preliminary data are strong and supportive of the proposed project. • The premise of combining a scaffold with a stem cell-derived neural cell therapy is sound for healing spinal cord injuries. • This study builds on a compelling prior study demonstrating the promise of a 3D printed scaffolds and stem cell derived neural progenitors in spinal cord injury treatment. Preliminary data for the cellularized scaffold in a preclinical model are supportive. • The use of neurotrophic factors released from nanoparticles to enhance cell survival is sound. • Preliminary data establish the ability to release the neurotrophic factor from nanoparticles but do not show effectiveness in aiding cell survival.
No: 6	• Nice preliminary data. • Lacking a target product profile. They could adapt the printing to meet the needs of a different indication. • Concerns about the design of the study and feasibility of the project. • Exciting and well thought out. Could use a better injury model, not complete transection. • Challenges in how this can be used; what is the clinical application? • Unfortunately, the experiments proposed do not mimic human spinal cord injury making it difficult to determine the applicability of these discoveries to the actual clinical need. The experiments are conducted on complete experimental transections, when the more important comparison for human injuries would be severe contusion injuries. • There are also concerns about an over-simplistic view of biomaterials optimization.
GWG Votes	**Is the project well planned and designed?**
Yes: 7	• This is a well-thought-through and well-planned project. However, it is not clear why the applicants are now proposing to use a T3 complete transection SCI while they previously worked on cervical contusion injury. Their explanation, although sound, raises the question about the translatability of findings, as mechanisms behind those two SCI types are different. • Relevance of the model for clinical translation is of concern. • The applicants stated they will use both male and female rats. Why is that? How many of each will be used? Power calculations taking sex into account should be provided. What is the age of the rats that will be used in the experiment? DRG age? Which exact behavioral testing will be performed and when exactly? • Optimization plan is not clear. • Potential pitfalls and possible alternatives are provided for all major steps.
No: 8	• Even if it works, how do you use the product? • There are concerns about the model (complete injury) which does not represent clinical SCI and thus lacks translatability. • There are concerns with the choice of a transection model rather than a contusion model, which would be more clinically relevant. • The preclinical model has unclear study design and unclear endpoints. • Wrong model - not translatable. Should not use a complete transection model.

	• The study lacks a systematic experimental approach. The Aim 1 design does not have a parameter variation strategy nor a clear assessment of properties other than number of open channels. • The study does not adequately leverage in vitro results to design the scaffolds for in vivo testing. • There are concerns about metrics for scaffold optimization. • Factor release study lacks a clear design criteria optimization approach. • There are concerns about the lack of proper controls. • A control of scaffolds with empty nanoparticles is missing. This is important given the concern that the nanoparticles may affect scaffold polymerization. • The plan has challenges with no optimization plan. What is the target product profile? • Greater depth also is needed on biomaterial optimization approaches, even though the design of the biomaterials is very interesting. • Analysis of differentiation paths of transplanted cells is unsatisfactory. • The number of animals to be studied seems very low, particularly considering variability of recovery in different animals. • The concerns are both obvious and are not discussed, and this raises some concerns about the thoughtfulness for progression.
GWG Votes	**Is the project feasible?**
Yes: 10	• This is a very ambitious project which requires high expertise levels. The applicants are experts in the field. However, due to the nature of the project and its very ambitious goals, the applicants may be understaffed. • Milestones for the in vivo assays are quantitative but the in vitro milestones are qualitative in nature. • In vivo milestones are set to match the cell-free scaffolds. They should be set higher to illustrate the benefits of cells. • The project is feasible as written, but the applicability of the materials is unclear, even if they work perfectly in the artificial model used.
No: 5	• Lack of a more relevant in vivo model. Why a complete transection model? Why not a more applicable contusion model? • Lacking key controls…no mention of the properties for the scaffold with nanoparticle.
GWG Votes	**Does the project uphold principles of diversity, equity and inclusion (DEI)?**
Yes: 15	• Yes. However, although the applicants state that the gender does not play a role in SCI regeneration they go on to say they will use both male and female rats. It is not clear if the proposed approach is actually meaningful and if the study is well powered due to the use of both sexes. • Patient groups/advocates not involved, and this would be not just desirable but necessary in SCI projects. • SCI is a greater problem for poor and minority populations, who may have more frequent injuries and poorer access to the best clinical care.
No: 0	• The proposal does not address how perspectives from various populations will affect the project or product development. • All members of the CA population suffer from spinal cord injuries. • The study will use male and female rats.

Application #	DISC2-15020
Title (as written by the applicant)	A Novel, Injectable, and Biodegradable Thermoresponsive Hydrogel for Improved Engraftment and Efficacy of Cell Therapy for Parkinson's Disease
Research Objective (as written by the applicant)	The therapeutic candidate is a combination cell (allogeneic midbrain dopaminergic neurons derived from H9 hESCs) and thermoresponsive engraftment biomaterial for Parkinson's disease.
Impact (as written by the applicant)	Survival of dopaminergic cells after implantation into Parkinson's disease (PD) brains remains extremely low (1-5%), and treatment benefits are only noticeable starting ten months to two years after transplantation.
Major Proposed Activities (as written by the applicant)	• Synthesize and optimize injectable thermoresponsive functionalized hydrogels • Characterize in vitro dose response and potency of thermoresponsive functionalized hydrogels on DA neurons • Assess acute toxicity of thermoresponsive functionalized injectable hydrogels in a mouse model • Evaluate in vivo efficacy of implanted DA neurons with thermoresponsive functionalized hydrogel in a PD rat model • Prepare first drafts of regulatory documentation
Statement of Benefit to California (as written by the applicant)	In California, Parkinson's disease affects over 90,000 adults, with correlations to individuals exposed to pesticides, such as those involved in CA's large agricultural industry. Cases are expected to increase 50% by 2030, amounting to a projected economic burden of more than $79B by 2037 in the U.S. This proposal to develop an effective combination cell + biomaterial therapy aims to alleviate this significant healthcare burden on Californians caused by PD.
Funds Requested	$1,482,500
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 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	3
Highest	79
Lowest	70
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 11	• The proposed therapy has a potential to generate an effective delivery strategy of human embryonic stem cell (hESC)-derived midbrain dopaminergic (DA) neurons to the substantia nigra of PD patients. The technology may improve the survival of these neurons and promote their functional integration with the host. The candidate will impact an unmet medical need. • The implantation technique, which involves the use of a hydrogel to deliver DA neurons, has yielded promising outcomes. Specifically, it has led to enhanced survival rates and expedited relief of symptoms in a rat model of PD. The integration of a neurotrophic factor into the delivery system results in improved viability, functioning, and selectivity of dopamine neurons. • The proposed technology is still in its early stages of development. A progression from the discovery to translational stage is outlined. • The proposed technology, if combined with cell therapy, could lead to better treatments for PD. • The findings could accelerate development of stem cell therapies for PD. • There is tremendous unmet need in PD. • It is unclear if this product is providing an improvement over current therapies.
No: 3	• The proposed product is complex and the multiple components (stem cells, biomaterial, growth factor) reduce translatability.
GWG Votes	**Is the rationale sound?**
Yes: 9	• The hypothesis that hESC-derived DA neurons can serve as an effective therapy for Parkinson disease has been previously demonstrated in animal models, and thus is based on a sound scientific rationale. An obstacle for translating this stem cell technology to the clinic has been the low rate of survival of the transplanted DA neurons in vivo. • The proposed project is based on sound scientific rationale when it comes to supporting survival via providing trophic support of grafted dopamine neuron progenitors as a means to increase effectiveness of stem cell therapies in PD. • The biomaterial component is well thought out, possibly due to the proportion of engineers on the team. • It is unclear if the neurotrophic factor is really necessary and helping cell survival. It is also unclear if the models are relevant to translation. • The rationale for accelerated treatment benefits or prevention of divergent differentiation is not clear. • There is a large amount of preliminary data in the application to support the feasibility of executing the experiments but they do not provide strong rationale for the basis of project. • Preliminary data to indicate that cell differentiation with good in vivo survival is achievable is missing. In addition, the presented preliminary data are not benchmarked to the current state of the art in the field and to approaches currently being tested in the clinic.
No: 5	• It is concerning that the preliminary data were generated with suboptimal cell transplant conditions, questioning the benefit that a hydrogel would provide in optimized transplant conditions. • The applicants have observed that hydrogels, when combined with a neurotrophic factor, enhance the viability of hESC-derived DA neurons at a 20-week interval following transplantation. However, it appears that HA alone also exhibits favorable outcomes in this regard, so the rationale for the neurotropic factor is not clear. • The extent of improvement shown with neurotrophic factor supplementation demonstrates variability. • The rationale for the hydrogel could be strengthened, and the role of the neurotrophic factor is not clear.
GWG Votes	**Is the project well planned and designed?**
Yes: 11	• The project is well planned and designed to address the goals of the proposed milestones, including the proof-of-concept studies. The applicants present a plan for advancing into translational studies, but the project is still in the discovery stage. Therefore, it carries an element of risk. • The project is well planned and designed. The expertise in biomaterials is obvious and well combined with strategy and cells.

	• The project takes a step-wise approach starting with synthesizing and optimizing the injectable thermoresponsive hydrogels, followed by testing the effect of the gels on cell survival and function. • All preliminary studies utilized preparations containing a non-injectable hydrogel, versus the injectable thermosensitive hydrogel proposed for this project. • The applicants state that the injectable hydrogels have already been extensively characterized and tested, and that this hydrogel plus neurotrophic factor should be superior in its performance to non-injectable hydrogels. This is a reasonable assumption, but the change in the delivery vehicle increases the risk of the project. • The complexity of the product is a concern from a regulatory and clinical development prospective.
No: 3	*none*
GWG Votes	**Is the project feasible?**
Yes: 13	• The milestones are logical, and it is realistic to achieve them within the proposed timeline. The team is highly qualified with all necessary expertise available. New experts added to the current application additionally strengthens the team. • The project is feasible given the expertise of the team. • The team is well composed but lacks in house expertise in in vivo models and interpretation of these models. • The budget is appropriate for the research proposed.
No: 1	• It is unclear whether the preliminary data really show that the neurotrophic factor contributes to survival. • The project involves a high risk in the use of a novel polymer with protein and cell components. This also entails massive regulatory hurdles. • The applicants propose a great research project, but it is unlikely to result in a clinical candidate.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 14	• The project is adequately designed to account for influence of sex and gender by including both female and male rats in the in vivo efficacy studies. The allogeneic DA neuron/biomaterial product resulting from this project will be applicable to any race/ethnicity. • Yes, DEI is taken into account when it comes to therapy development. One cell line will be used, but the applicants provide good rationale for this. • The proposed project has potential to inform the development of a product or tool that serves the unmet medical needs of the diverse California population, including underserved racial/ethnic communities, but whether this can be achieved is unclear at the moment.
No: 0	*none*

Application #	DISC2-14938
Title (as written by the applicant)	The implantable Bioartificial Pancreas (iBAP)
Research Objective (as written by the applicant)	This project's goal is to develop a new cell encapsulation system holding stem cell-derived pancreatic islets for treatment of Type 1 Diabetes.
Impact (as written by the applicant)	The cell encapsulation system will treat the over 600,000 Type 1 Diabetes patients in the United States who do not achieve adequate glucose control.
Major Proposed Activities (as written by the applicant)	• Develop a clinically-therapeutic scale device. • Develop a scaffold to house the stem cell-derived pancreatic islets to ensure proper function. • Evaluate the encapsulation device in pigs with Type 1 Diabetes.
Statement of Benefit to California (as written by the applicant)	Type 1 Diabetes (T1D) affects almost 225,000 Californians and incurs great costs for the State annually. Moreover, there are significant disparities in patient outcomes and access to treatments between different socioeconomic and ethnic groups. The encapsulation device being developed in this CIRM project will widen treatment access, improve patient lives, and reduce the overall costs of T1D.
Funds Requested	$2,719,424
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	72
Median	70
Standard Deviation	7
Highest	85
Lowest	65
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	1
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 13	• The goal of this application is to develop an implantable immunoprotective intravascular Bioartificial Pancreas (iBAP) for treatment of Type 1 Diabetes (T1D), which will

	encapsulate hPSC-derived islets (SC-islets) and will be equipped with a high hydraulic permeability/fast ultrafiltration rate silicon nanopore membrane (SNM). • The implantable Bioartificial Pancreas (iBAP) encapsulating stem cell-derived islets could address current issues of beta cell replacement that include suboptimal transplant site, immunoprotection, and cell sourcing and device refillibility/retrieval. • The design of this iBAP device is well-thought and backed up by years of experience in artificial kidney devices by a team with the necessary expertise to solve such a complex problem of intravascular islet-delivery devices. • The concept makes sense and there is the unmet need. • If successful, the proposed technology will be highly significant and will impact an unmet medical need. However, there are numerous risks that could impact the likelihood of success. • Intravascular devices may not demonstrate clinical translatability, which would diminish impact. • The impact is uncertain, as the approach has limitations outlined below.
No: 1	• The potential complications of intravascular devices limit the impact.
GWG Votes	**Is the rationale sound?**

Yes:
11
	• The project is based on a sound scientific rationale that achieving immune protection, physiologic oxygenation and glucose-insulin kinetics of the SC-islets will facilitate their long-term survival and function in vivo.
	• Intravascular macrodevices for islet delivery and immunoprotection address the issues of immunoprotection and enhanced nutrient/insulin/glucose diffusion. The proposed device has higher feasibility than previous attempts.
	• There is a lack of preliminary data to support the claim that the devices provide immunoprotection.
	• Diabetes reversal with SC-islets in diabetes large animal models remains to be optimized.
	• The preliminary data are abundant, but some results fall short in providing strong support for the project because they may not translate to in vivo efficacy or are not adequately controlled. Specifically:
	  • The collaborator on the project can consistently generate SC-islets from hPSCs using a directed differentiation protocol. These SC-islets will provide insulin-producing cells source for incorporation into iBAP.
	  • The SNMs have high hydraulic permeability, which is increased with larger pore size; also, SNMs exhibit anti-fouling activity (with appropriate coating) and have better hemofiltration properties compared to conventional polymer membranes.
	  • The SNM (smaller pore size) shows immunoprotection of the SC-islets. However, this result is unconvincing because it is based on a 6h in vitro assay, which is not expected to be reflective of an in vivo situation.
	  • The SNM (larger pore size) provided improved islet viability under conditions of convective mass transport vs. simple diffusion in 3 day in vitro assays. This in vitro result is also unconvincing as it is unlikely to be informative about islet viability in vivo.
	  • SC-islets seeded in a superporous agarose (SPA) cell scaffold and encapsulated in SNM demonstrate appropriate glucose stimulated insulin secretion (GSIS), absolute insulin production rates, and viability in vitro. SPA was employed to minimize the diffusion distance between the ultrafiltrate and SC-islets. The SNM pore size in these experiments was not defined. No comparison was shown with non-encapsulated SC-islets.

No: 3	• The concept of vascular graphs for delivering islet stem cells is a good concept, but has challenges for clinical translatability and long-term efficacy.
GWG Votes	**Is the project well planned and designed?**
Yes: 8	• The applicants propose a step-wise approach to optimize iBAP design to maximize nutrient/insulin/glucose transport through experimental and computational tools and test it in vitro with SC-islets and in vivo in a diabetic large animal model. • Methods, analysis, and quantitative expected outcomes are well described. • There is limited discussion of translation to the clinic, which raises concerns that the product is not translatable.

	• The feasibility of xenoprotection by iBAP devices is low and the possibility to include immunosuppression is not described. • Though mentioned, there is no description on how alloantigen sensitization in large animal models will be measured.
No: 6	• The PI has been previously funded by CIRM for a related project, and in 2017 the PI's lab published a manuscript supporting the concept for this work. • It is evident that SNM-based iBAP studies are not new; they have been pursued in the PI's lab for a number of years and the outcome so far has been modest, with only in vitro or short-term in vivo proof-of-concept results generated. This situation undermines potential translatability of the proposed technology. • While many technical design principles of the iBAP device will be optimized and tested, the biological questions of how to optimize iBAP for its function in vivo to provide long-term cell survival and function without immunosuppression are not sufficiently addressed. • The proposal requires additional supporting preliminary data, and particularly in vivo data. • The application does not adequately address alternative approaches to be used if the long-term survival and function of the SC-islets in vivo is not achieved using the proposed strategy. The only possible solution the PI proposes is to increase the SNM's pore size to improve the grafts' oxygenation. This strategy, however, may compromise the in vivo immunoprotection of iBAP-encapsulated allogeneic SC-islets and thus might not provide a viable solution.
GWG Votes	**Is the project feasible?**
Yes: 9	• The application has clearly described milestones with a strong plan to achieve them. • The project will be conducted in an excellent environment and with an excellent team for device design/testing, SC-islet inclusion, immunological studies, and translation. • The milestones are logical, but the project remains highly risky. • Overall, the team is appropriately qualified and staffed. However, it is not clear if immunology expertise on the team is sufficient.
No: 5	• Potential challenges for clinical translatability and safety, in particular the invasiveness of the approach and thrombotic consequences, may limit feasibility.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 14	• The project's plan adequately addresses the influence of race and ethnicity on the outcomes of T1D. If successful, this project will result in a new universal stem cell therapy that would be applicable to the members of all racial and ethnic groups. • The proposal includes adequate considerations of DEI. • This universal stem cell-based therapy will serve the unmet medical needs of the diverse California population including the underserved communities. • The applicants point out that there is a higher T1D incidence among certain racial and ethnic populations and outcomes disparities are also present in these groups.
No: 0	*none*

Application #	DISC2-14892
Title (as written by the applicant)	Allogeneic Stem Cell-Engineered CAR-NKT Cells Targeting CD70 for AML Therapy
Research Objective (as written by the applicant)	HSC-engineered allogeneic CD70-targeting CAR-NKT (AlloCAR70-NKT) cells
Impact (as written by the applicant)	Treatment of acute myeloid leukemia (AML)
Major Proposed Activities (as written by the applicant)	• Milestone 1. Generation of the candidate AlloCAR70-NKT cell products • Milestone 2. Characterization of the candidate AlloCAR70-NKT cell products • Milestone 3. Delivery of the new therapeutic candidate
Statement of Benefit to California (as written by the applicant)	Acute myeloid leukemia (AML) is the most common acute leukemia in adults. In 2023, it is estimated that about 20,380 new cases of AML will be diagnosed and about 11,310 deaths from AML will occur in the US. Notably, California is one of the leading states with the highest deaths from AML. Therefore, novel therapies are urgently needed to save Californian lives.
Funds Requested	$2,364,000
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: 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	5
Highest	80
Lowest	65
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 12	• AML represents a major unmet medical need and development of cell-based immunotherapy is one of the promising approaches. • An allogeneic cell product could meet unmet needs for AML.

	• CD70 is a clinically validated target in AML. CAR-NKT therapy targeting CD70 is expected to be safe and could be more effective than previously tested therapies including CD70-specific antibodies and CAR-T cells. • The expected candidate will likely be selected for a clinical trial of an HSC-derived CAR-NKT product in patients with AML and possibly with other CD70-positive malignancies. • The envisioned product consists of several key elements that will be optimized in the course of the project to providing multiple alternatives, including CAR construct design, a choice of co-expressed cytokines, suicide switch, and control of HLA expression. There is a clear plan and logical sequence for product optimization and selection of the lead candidate for clinical testing. • CAR CD70-NKT cells have been generated in large numbers from cord blood hematopoetic stem cells using a clinically compatible protocol and have shown to be highly functional. The data is compelling and provides a proof of concept for the project. • Two similar candidates are already in the clinic, so the approach in this proposal is not novel. To this end, the investigators could use their knowledge based on the other two candidates to assess the regulatory process, rather than through an INTERACT meeting.
No: 2	• The application builds on prior work that has established production of stem-cell derived iNKT, which are promising because they don't cause graft vs. host disease but are present at very low numbers in human adult blood. • This application proposes cord-blood derived iNKT cells lenti-transduced to express a CD70-targeted CAR and secrete human IL-15. The potential clinical indication is relapsed/refractory AML that highly expresses CD70. The product will be given as a single dose. The unmet medical need is definitely present in relapsed/refractory AML. • One weakness is that the last milestone is an INTERACT meeting with FDA, which is still far from a clinical candidate and is not likely to be very informative given that there are two other iNKT products already further ahead in development by this group. • Much of this proposal is redundant with other previously published and developed CD70 CARs, both from academia and industry. By the time this product gets to the clinic, there will have been many trials of CD70 CARs. • Although the final product proposed is new, the components lack novelty (CD70 CAR designs are not innovative, and the applicants use other groups' published designs; secreted IL-15 is not new; CRISPR editing of B2M is not new, nor is editing of CD70). The iNKT platform derived from cord blood is a significant innovation but has not yet been tested in CD19 or BCMA and is already licensed. A concern is that this will not progress to IND due to safety. • The proposal only superficially covers many potential safety issues.
GWG Votes	**Is the rationale sound?**
Yes: 7	• NKT cells have several advantages over conventional T cells as a platform for CAR-redirected immunotherapy, including high cytotoxic potential against tumor cells, targeting CD1d-positive tumor-associated macrophages, and the lack of alloreactivity. • There is a solid support in the literature and preliminary data for inclusion of IL-15 as a lead candidate cytokine to be co-expressed with the CAR in NKT cells. There is also a plan for testing alternative cytokines. • CAR-NKT cells can be used for off-the-shelf immunotherapy without a risk of graft vs. host disease. This is a major advantage over CAR-T cells that cannot be used from allogeneic sources without additional genetic manipulations. • Preliminary data indicate that CAR-NKT cells have superior in vitro and in vivo antitumor activity in AML models compared with CAR-T cells. These results provide a strong scientific premise for the project. • CAR-NKT but not CAR-T cells kill M2 macrophages, providing additional experimental support for potential advantage of CAR-NKT for targeting immune suppressive tumor microenvironment. • HSC-derived CAR-NKT show low levels of HLA expression, suggesting that they could be resistant to host-mediated rejection. There is a plan for an alternative approach targeting additional genes with CRISPR for further downregulation of class I and class II expression.
No: 7	• The proposal leverages cord-blood derived cells and the applicant's unique method of using these to produce iNKT.

	• The feeder-free/serum-free ex vivo culture method for HSC-derived CAR-NKT is a strong system, although it has not yet been tested with cord blood. • It is concerning that the multiple gene modifications will require a prolonged culture system. • The advantages and actual feasibility of allogeneic cord-blood derived iNKT cells are not clear, especially with regard to multiple gene edits and enhanced functionalities. This prompts concerns about safety and feasibility. • The preliminary data consist of cartoons and some true data, but much of it is equivalent to what can be done with mature PBMCs instead of focusing on the safety concerns of the allogeneic cord-blood derived multiplex gene edited and transduced cell product proposed here. • Critical preliminary data are missing. • The class I and class II expression needs to be addressed more clearly.
GWG Votes	**Is the project well planned and designed?**
Yes: 5	• The project is well planned and the key proof-of-concept data already exist. Cord blood is an appropriate source of allogeneic HSC cells in this project. • There are appropriate controls, model systems, and statistical considerations. • Several pitfalls have been identified and there are plans to address them including hinge design in the CAR construct, choice of a co-expressed cytokine, suicide switch, and control of HLA expression to avoid graft rejection. • HLA class I downregulation can make NKTs susceptible to killing by allogeneic NK cells. Testing for NK cell alloreactivity should be added to the experimental plan. • Considering a potential for IL-15 to support antigen-independent NKT cell proliferation, an autonomous growth assay should be developed. • The preliminary data show NKT-mediated killing of M2 macrophages. It would be important to test the selectivity of NKT killing of M2 vs. M1 macrophages.
No: 9	• The preliminary data need to be obtained using more relevant models and cell products. • It is not clear that the proposed studies will lead to the next steps for translation. There is a sense that the applicants are proposing the experiments that are most feasible versus those that are most necessary. • This proposal may be premature. In particular, the applicants reference another group's interim safety analysis of a phase 1 clinical trial of a secreted IL-15 gene in a totally different CAR product in a totally different disease, which is not enough to consider the safety of secreted IL-15 in their product. It is not clear how they will make a decision as to whether to proceed with IL-15 or not, and what would prompt the use of a suicide gene or which gene would be chosen. • The proposal seems to use a first generation, ligand-based CAR targeting CD70, which has been tested in other settings with limited efficacy results. • The proposal does not test for susceptibility of low-MHC cord-blood derived iNKT to be killed by mature NK cells, especially when induced to grow by IL-15. • It is commendable that the applicants considered fratricide, but they should think beyond fratricide of the product, as it could also impact on-target toxicity towards the hematopoietic compartment overall, and stem cell graft of an allogeneic donor. • The CAR designs and other aspects of their strategies may be difficult to actually implement and translate if they are based on patented designs of others. • It is concerning that the approaches are redundant with little innovation of construct design. • The CAR design is not innovative. • Aspects of their approach have been out licensed to industry partners and progress seems to be slow, meaning that this product will be behind in reaching the market.
GWG Votes	**Is the project feasible?**
Yes: 8	• There is already a solid amount of preliminary data, making the project highly feasible and achievable within the timeline. • The PI has an excellent record of publications on the development of HSC-derived NKT and CAR-NKT cells for cancer therapy. The PI and their team are uniquely qualified for the project. • The PI and team have access to required materials, reagents and models to accomplished proposed studies.

	• The budget is appropriate. • The team is in a good environment and capable of doing the proposed studies.
No: 6	• The team, and particular the advisors, have impressive expertise. • The team is in a strong location, with supportive facilities and an intellectual environment. • There is no history of this team or the company with which they are partnering of actually opening an IND and leading clinical trials. Much has been spent on pre-clinical development, but their expertise has not really been stress-tested yet in the form of an IND submission or patient enrollment. • The applicants have many prototypes of allogeneic cord-blood-derived NKT products with different CARs, but none yet in the clinic (CD19, BCMA, now CD70). • The applicants have not addressed how they are identifying donors, especially for underserved populations. • For this amount of funding, getting closer to an IND would be expected.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 13	• The project plan and design adequately address and account for the influence of race, ethnicity, sex and gender diversity. • The applicants intend to enroll at least one out of three patients from underserved populations.
No: 1	• The applicant plans to include and enroll participants from outside sites that serve diverse communities. • There are plans to enroll at least one third of patients at a hospital that serves underserved populations, but the applicants have not addressed the feasibility or safety considerations for this phase 1 study of a high-risk product in a high-risk disease as it relates to the target enrolled patient population. • The applicants have not considered that patients probably will need to have an identified allogeneic HSCT donor ahead of time, and that it can be quite difficult to find such donors in certain populations. • There a variety of biologic issues at play (diversity of HLA types and difficulties associated with post-CAR allogeneic transplant) with this product, which are not necessarily the fault of this proposal.

Application #	DISC2-14893
Title (as written by the applicant)	A novel bioinformatic strategy to generate cervical V2a interneurons for spinal cord injury (SCI) engraftment
Research Objective (as written by the applicant)	We harness unique bioinformatic strategies to drive a neural stem cell (NSC) towards an excitatory interneuron progenitor fate. Machine learning will further map its phenotypic trajectory to maturity.
Impact (as written by the applicant)	Identifying transcription factors that drive a cell's fate remains a challenging task and critical bottleneck for cellular conversion. Here we use modern tools of neuroscience to overcome this barrier.
Major Proposed Activities (as written by the applicant)	• Design, optimize, and develop delivery of phenotypic transcription factors for lineage specification. • Drive H9 spinal cord neural stem cells (H9 scNSCs) toward a V2a neural progenitor fate in a temporally and concentration controlled manner. • Transplant V2a progenitors into spinal cord injury (SCI) lesions and optimize transplantation parameters and V2a maturation trajectory. • Assess translational efficacy of therapeutic cellular product through behavioral assessment and histological analysis in a C5 bilateral contusion model of SCI.
Statement of Benefit to California (as written by the applicant)	The proposed allogeneic cell product will be equally applicable to all patients suffering from spinal cord injury (SCI). This includes all race, ethnicity, gender, sexual orientation, gender identity, age or any other factor reflecting the diversity of California's population.
Funds Requested	$2,376,000
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: 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	2
Highest	79
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 14	• Spinal cord injury (SCI), particularly cervical SCI, has high unmet medical need. Various therapies have been proposed, among which cell-based ones, as proposed by the applicant, have been particularly promising. • C5 contusion spinal cord injury has huge unmet need. • SCI is a significant problem and cell therapy is a promising avenue. The applicant proposes studies that test their approach using relevant models of the cervical injuries that are the most challenging and devastating. • The proposal puts forward a relatively novel bioinformatic strategy to generate cervical V2a neural progenitors for SCI engraftment. • There are very limited therapies for severe SCI, which is especially debilitating in the cervical region. If the applicant can successfully grow and implant V2a neural progenitors in humans, this project would represent a potentially curative therapy. That said, the degree of expected improvement remains uncertain and is likely related to success of graft implantation. Success of implantation is subject to the usual immune, oncogenic and cell viability pitfalls. • Overall, yes, though the use of the proposed animal model (athymic nude rats) limits translation to clinical settings. • The use of athymic nude rats that lack T cells limits translational power, especially in light of recent data that suggest protective and destructive roles during the recovery process. Athymic nude rats show delayed tissue death but limited long-term recovery from moderate SCI compared to non-immunocompromised rats which is associated with compensatory features of the immune response. • There is no clear plan for progression to translation - only a general statement that if successful, the project could translate to trials. • This project is ambitious in that the neurons (in their final, therapeutic form) can't yet be made. It is therefore potentially far from translation, which may be why the applicant is not concrete in their description of future plans for translation. • A current CIRM TRAN awardee is also investigating H9 spinal cord neural stem cells (H9 scNSCs) for therapeutic use in SCI. That project is already on the way to translation. Improvements to existing approaches are valid, but this applicant does not define a clear, urgent bottleneck.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 8	• The applicant has successfully generated H9 spinal cord neural stem cells (H9 scNSCs) and shown preliminary therapeutic efficacy in spinal cord injury (SCI) in a large animal study. In these studies, cells from the H9 scNSC grafts formed synapses with host neurons, indicating their potential for functional integration into the host spinal cord circuitry. The applicants suggests that optimization of this stem cell therapy may maximize therapeutic benefits. • Transcription factor based reprogramming has shown robust effects and seems to be superior to reprogramming by exogenous factors. • The rationale that cell purity in the H9 scNSC graft would increase efficacy is not clear. In fact, in previous work the applicant points out that an important aspect of the success of their transplant was that their NSC grafts can yield a broad range of identified spinal cord neuronal phenotypes, as well as cardinal glial cell types. Why would narrowing this broad spectrum of cells be more efficacious? • Instead of starting with stem cells the proposal uses re-programmed cells. This is a change from the applicant's previous work, and is not adequately explained. • The potential impact of inflammatory responses to the graft is not addressed.
No: 7	• Overall, the project has a straightforward rationale: growing and implanting a type of neuron that is important for nerve conduction in the wounded spinal cord. • The rationale is only partially sound. The applicant has generated an H9 scNSC graft and shown efficacy in SCI in a large animal study. The grafts showed potential for integration into the recipient's spinal cord circuitry. • It is not clear how efficacy will be increased by limiting the cell types generated by the H9 scNSC graft. The applicant does not provide sufficient details about the animal model to

	be used (except that they will use females), e.g. age, exact experimental protocol, testing, and power calculations. These are essentials for such a proposal. • In order to produce the desired type of neuron, the applicant will need to carefully guide differentiating cells down a path that NSCs are not inclined to go down, at least in current protocols. • The method utilized for selection of V2a fate-promoting transcription factors (TFs) is not well-validated and rarely used by other labs. The method focuses on finding synergistic effects among multiple TF's, and can therefore fall short if the initial dataset does not include a full set of interdependent TFs. The applicant should propose other computational methods to validate or invalidate the selection of TFs. • The applicant's plans for identification of transcription factors (TFs) that will push stem cells into the V2a lineage look promising. The methodology for selecting TFs is reasonable, though not widely used. However, computational selection of regulatory genes for differentiation is longstanding and unsolved; it's unlikely this single method will return the combination of silver bullets. • There are a number of concerning issues regarding rationale, experimental design, and preliminary data. • It's not clear how the proposed approach would be better than previous/current approaches.
GWG Votes	**Is the project well planned and designed?**
Yes: 9	• The applicant used single nucleus RNA sequencing (snRNAseq) of human fetal spinal cord tissue and interneurons at the adult stage to identify marker profiles that would distinguish V2a excitatory neurons from inhibitory V2b and V2c interneurons. An overlapping cluster of cells was found and RNA sequencing bioinformatics identified candidate transcription factors that could drive conversion of NSCs to V2a excitatory neurons. • This is well designed and includes elegant studies on making V2a excitatory neurons. • Aim 1 is a strength. • The in vitro, transcription factor guided approach is sophisticated and well-designed. However, the advantages of the proposed approach (in relation to existing ones) are not very clear. The application does not include adequate discussion of pitfalls. • The applicant's planned attempt to achieve temporal sequence of expression is a strength, though the method is unproven. • The proposal should include in vivo data showing cell survival.
No: 6	• Use of lipid nanoparticles to deliver mRNAs is a nice way to decrease oncogenic concerns. • The project comprises a great deal of work: differentiating a specific neuronal type (without a validated protocol, yet) through conducting functional assays in a transplant model. The applicant has a reasonable (though possibly optimistic) set of milestone for the full process. • If the TFs predicted to generate the V2a neurons aren't validated in the proposed work, what next? Predicting combinations of genes to control cell fate isn't routine or easy, and back up methods are not proposed.
GWG Votes	**Is the project feasible?**
Yes: 8	• This project depends on the generation of V2a neurons. The applicant is proposing the use of a single (not fully validated) method to choose the right transcription factors (TFs). This is a high-risk approach without proposed alternatives. • The applicant is qualified, but additional team members need to be recruited. Testing efficacy in the last year of the project - potentially without expertise on the team - makes success unlikely. • The expected outcome for in vivo transplantation is not clear. How will additional efficiency be defined? • Maybe. Staff need to be recruited to conduct this complex work. Previous published work shows the applicant's competence in the approach, though the applicant was not part of the most relevant paper that is cited throughout the application. This leaves open questions as to the role of the applicant in prior work and their expertise in the transplantation and behavioral approaches. • A team member with relevant expertise needs to be hired.

No: 7	• Very little is known about the re-programmed cells to be transplanted. Are they stable? Functional? • The project prioritizes cell work (2 years) over efficacy work (1 year). • The TF validation methodology is not adequate. • There's a strong possibility that this project will not generate V2a neurons. This is because the applicant will make assumptions in their selection of TFs that may not prove valid, and other approaches will be needed to identify relevant TFs. This will significantly delay the timeline.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 14	• The applicant's point about higher rates of re-admission in Black and Hispanic populations has tenuous applicability to SCI, but the higher mortality seen in Black patients and the substantial costs of rehabilitation efforts are relevant. • Only female rodents are used for transplantation despite the fact that 80% of injuries occur in males. The applicant's rationale for excluding males (to minimize bladder infections) is logical, but the resulting data will be limited. • DEI topics were explored in a general way. The project has limited involvement of patients which is highly recommended for SCI-related projects. • The originating tissue samples come from a broad population. • DEI is addressed in a limited way.
No: 1	*none*

Application #	DISC2-15008
Title (as written by the applicant)	Off-the-shelf stem cell (SC)-derived, hypoimmunogenic "synthetic islets" for reversal of diabetes
Research Objective (as written by the applicant)	Create "Synthetic Islets" from gene-edited embryonic and umbilical stems cells that are safe and can reverse type 1 diabetes and evade immune rejection.
Impact (as written by the applicant)	Creating an "off-the-shelf" stem-cell-derived cell therapy ("synthetic islets") that is safe, does not require immunosuppression, and can be broadly applied to all diabetes patients.
Major Proposed Activities (as written by the applicant)	• Insert a suicide gene into embryonic stem cells to eliminate risky cells and confirm that gene editing does not interfere with cell development and function before & after transplant. • Inactivate another gene in the above cells to block risky serotonin production. • Establish methods for mixing with umbilical cord stem cells to improve islet transplant survival and protect from rejection when transplanted into mice. • Establish safety and effectiveness of gene-edited stem cell islets alone and mixed with umbilical cord stem cells in mice. • Test other gene edits to the embryonic stem cells to evade recognition by the immune system and avoid need for immunosuppression medications. • Analyze all blood/collected tissues to establish safety and effectiveness of the product and prepare final reports.
Statement of Benefit to California (as written by the applicant)	Diabetes affects more than 3.2 million Californians (~10% T1D). T1D is burdensome to manage, requiring non-stop blood sugar monitoring and insulin injections to survive. Achieving good blood sugar control is difficult and complications are frequent. Diabetes and its complications cost Californians $39.5 billion/year, plus $12.5 billion in lost productivity. Creating gene-edited synthetic islets offers safe and effective therapy to replace insulin and without the need for immunosuppression.
Funds Requested	$2,263,502
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	80
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 13	• The project aims to create hypoimmunogenic synthetic islets to broaden the potential clinical application of SC-islet therapy for diabetes, addressing a significant unmet medical need. • The project seeks to combine multiple approaches to create hypoimmunogenic synthetic islets, potentially reducing risks and costs associated with transplant and immunosuppression, thus accelerating stem cell therapy for diabetes. • It is uncertain whether the project will result in a successful candidate. • A concern is the applicant gene editing approach, which is very likely to be silenced during beta cell differentiation.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 8	• The preliminary data showed supportive results when the applicants used established cell lines. However, in the experimental design section, the applicants do not seem to be experts in gene editing. Some of the designs may not be compatible with the new technology and could end up with extremely low efficiency. • A complicated approach is described.
No: 6	• The rationale is questionable in the basic premise of the project. • The cited supportive preliminary data are not from the applicant. • The proposed strategies may not be sufficient to block allorejection and recurrence of autoimmunity. • The pre-vascularized subcutaneous site is poorly described and data showing diabetes reversal are not provided. • Clinical data and NOD mouse model data are provided, which are not strictly relevant to the proposal. • The applicant team is lacking expertise for transgenic gene editing. • The application is not the most up to date on gene editing and integration with lentivirus; and the proposed approach is not a viable option as a clinical candidate.
GWG Votes	**Is the project well planned and designed?**
Yes: 7	• The project includes milestones and tasks, including the development of hypoimmunogenic synthetic islets derived from specific cell lines, and evaluation in various models. • The planned approach to address the allogeneic rejection may not work at all. • For PDL1, the applicant plans to use lentivirus for integration. This is a major concern because the lentivirus may be silenced during beta cell differentiation. • The applicants did not outline sufficient potential pitfalls or alternative approaches.
No: 7	• There is low feasibility of subcutaneous and omental transplantation due to limited preliminary data. • The feasibility of testing in a T1D humanized mouse model is low due to lack of preliminary data in this specific model. • The use of lentivirus is a concern. Due to random integration into the genome, clinical translatability is a large concern. • The proposal is very ambitious. • Preliminary data included in the proposal are weak.
GWG Votes	**Is the project feasible?**
Yes: 9	• Some of the milestones, especially the gene editing part, may not be feasible for this team. A gene editing expert is needed for this team. • It is unclear whether the milestones will be completed in the timeline proposed.

	• The team, resources, and budget are feasible.
No: 5	• The viral vectors to be used raise concerns. • The proposal is overambitious. • Genetic engineering id feasible given the preliminary data, but in vivo testing may be less feasible due to limited preliminary data. • The application originates from strong PIs and a strong organization, but the lack of viral vector expertise on the team is apparent. • The use of lentivirus is a concern for future viral vectors. The required level of expertise and technology to accomplish this proposal is lacking. • The applicants are using technologies that are coming from other outside researchers, which raises concerns for replication capabilities.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 14	• The project aims to address diabetes, which affects a diverse population, including increasing rates of T1D diagnoses in minority groups. • The study team includes a member living with T1D, and the team is actively engaged with local patient-centered organizations, gathering broader perspectives. • Properly discussed.
No: 0	*none*

Application #	DISC2-14977
Title (as written by the applicant)	An immunoprotective bioreactor for stem cell-derived renal tubule cells enabling an implanted bioartificial kidney
Research Objective (as written by the applicant)	This CIRM DISC2 project is developing a stem cell enabled bioreactor to enable an implantable bioartificial kidney.
Impact (as written by the applicant)	End-Stage Renal Disease (ESRD) and shortage of donor organs. Patients would receive an implanted, continuous operating, artificial kidney instead of having to receive dialysis or wait for transplant.
Major Proposed Activities (as written by the applicant)	• Create the scaffolding material to ensure proper growth and function of stem cell-derived kidney cells on silicon membranes without the need for immunosuppression therapy. • Create and test an implanted bioreactor component of the artificial kidney. The bioreactor will encapsulate the stem cell-derived kidney cells enabling function without immunosuppression therapy.
Statement of Benefit to California (as written by the applicant)	Kidney failure affects a significant number of California citizens and incurs an extremely high cost on the local California healthcare system. This CIRM DISC2 project will create a bioreactor component of the artificial kidney.
Funds Requested	$631,250
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	5
Highest	85
Lowest	65
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 project hold the necessary significance and potential for impact?
Yes: 13	• The unmet clinical need is great and clearly articulated. Indeed, the development of the implantable bioartificial kidney (iBAK) has been a visible project over a number of years extending from the initial data generated around renal assist devices several decades ago. A transplantable immuno-protected device would be a major advantage. • The project addresses an unmet medical need. Kidney conditions lead to numerous individuals dying without the necessary treatment, and current solutions such as dialysis present challenges. The development and potential of the iBAK technology in the context of renal assist devices from decades past is noteworthy. • The concept of a cell-containing device to assist in renal function is not a new one. Indeed, this proposal draws on considerable prior research, including clinical trial, for the use of renal assist devices into which cadaveric epithelial cells were present. The current approach includes a filtration element and claims to add stem cell-derived cells. • Artificial kidneys are sorely needed. • There is significant mortality associated with failure to receive necessary treatment for kidney disease, amplifying the unmet need. • The critical bottleneck that this proposal suggests they will address is the use of a robust expandable source of appropriate cells. The milestones only address this and evaluate appropriate blood flow and immunoprotection of such cells post transplantation.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 8	• The overall idea of having cells manage certain specific innate functions while providing a structural framework for them in the artificial kidney makes sense. There are intersecting technological and biological (stem cell, genomic, functional, transplantation) aspects to this project, and the applicants provided preliminary data for the main two parts of kidney function.
No: 6	• The choice of cell type needs to be better justified. • The proposal focuses largely on the device and does not adequately consider stem cells. • The biologic portions of the proposal feel underdeveloped. • The team is more device-focused rather than stem cell-focused, and a more comprehensive approach is needed to provide adequate rationale. • The rationale argues that the provision of stem cell-derived renal proximal tubule epithelium will be able to provide fluid and solute reabsorption. However, the proposed research will not be able to show proof of concept for this claim.
GWG Votes	**Is the project well planned and designed?**
Yes: 7	• This is part of a (necessarily) sprawling project by the premier artificial kidney project group, and as such it is well calibrated for human donors. The applicants are tackling the two major functions of kidneys claimed to not be replaceable with drugs, so this emphasizes the importance of a device. It's not clear to what extent additional blood filtration will be required, as the proposed product is trying to replicate two of ten kidney functions.
No: 7	• A major problem with the project is the lack of clarity on the cell types available from stem cells, what functional features these cells will require and how they will be evaluated before and after transplantation. There is also no discussion about scale up. Unless the right cells are available and can perform the functions they are intended to deliver, immunoprivilege is irrelevant. • If the project fails to generate the appropriate renal epithelial cells, then the plan reverts to the prior renal assist device (RAD) technology of utilizing cadaveric cells. No alternative process is detailed. Indeed, little details are provided on the process for generating renal cells. • The preliminary data rests on the device features. This draws on many years of development of RAD technology. There are no preliminary data provided on the stem cell-derived renal epithelial cells from a stem cell source. • There are concerns about the cells to be used in the device and logic of the experimental design. • The biological aspects of the project need to be strengthened.

	• The proposal lacks sufficient stem cell characterization. • Clarity on requirements for any additional blood filtration and the complete replication of all kidney functions is needed.
GWG Votes	**Is the project feasible?**
Yes: 7	• The investigators on this application are the most likely group to successfully undertake this proposal. • Not all aims appear feasible. Due to the lack of stem cell expertise and characterization, the likelihood of success of cell expansion is not clear. • The data-sharing plan is unrealistic and the lack of details makes it hard to evaluate. Exactly when will data be shared and to what extent? It is insufficient to say that data will be available in journals, when the project is likely to generate technical notes and measurements that will be important to share on sites such as github.
No: 7	• The applicants have established the necessary collaborations that can move the project forward. • The experimental design lacks detail and data to support undertaking this work. • As noted above, the genuine functionality of the cells used is of concern. Simply showing they are viable and have tight junctions is insufficient characterization. Understanding their functional identity is important for their required role. • The cell portions of the project are too preliminary. • It is not clear that the right cell types are available and will be tested in this proposal. All stem cells are to be provided by one of three collaborators. Each of these groups are generating completely different cell types. None of these groups have demonstrated an ability to generate mature functional proximal tubular cells. Indeed, even the collecting duct protocols show limited maturation to date. This makes function unlikely. • There is no stem cell biologist listed in the team and no evidence that this team has expertise in differentiating stem cells to kidney.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 14	• ESRD affected high proportions of various underserved groups, who would theoretically benefit from this device. • There have been exceptional outreach efforts. • The applicant team has a patient advisory group who have been giving input into design and patient requirements. • The team has made commendable outreach efforts to incorporate perspectives and experiences from the potential beneficiary population.
No: 0	*none*

Application #	DISC2-14905
Title (as written by the applicant)	Stem Cell-Derived Exosomes with Focused Ultrasound for Treatment of Chemotherapy-Induced Brain Toxicity
Research Objective (as written by the applicant)	Our objective is to determine the preclinical efficacy of human neural stem cell (NSC)-derived exosomes in combination with low intensity focused ultrasound (LIFU) to promote recovery from neuroinflammation in murine models of methotrexate-induced chemobrain.
Impact (as written by the applicant)	The proposed studies will begin an evaluation of NSC-exosome therapy in combination with LIFU, by providing a non-pharmacological approach with potential to restore brain cells and function.
Major Proposed Activities (as written by the applicant)	• Generate and characterize large neural stem cell and exosome research banks • Establish optimal parameters focused ultrasound to enhance distribution of neural stem cell-derived exosomes to the brain in preclinical models of chemotherapy induced brain toxicity ("chemobrain") • Generate exosome profiles and characterization for neural stem cell-derived exosomes using genomics and proteomics • Conduct in vivo therapeutic efficacy studies with LIFU and IV exosomes in preclinical models of acute chemobrain. • Conduct in vivo therapeutic efficacy studies with LIFU and IV exosomes in preclinical models of chronic chemobrain.
Statement of Benefit to California (as written by the applicant)	The number of cancer survivors continues to increase in the United States due to the growth of aging population as well as advances in cancer treatment. More than 18 million Americans with a history of cancer were alive on January 1, 2022 and about 100,000 people were diagnosed with cancer yearly in California. More services are needed for these patients, especially in the rural areas of California, that will address research, leading through translation of new long-lasting treatments for all.
Funds Requested	$2,240,088
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	4
Highest	78
Lowest	65
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 12	• The overall goal is to provide a novel (in the context of this condition) treatment for a condition generally known as chemobrain, which are the negative cognitive effects of chemotherapy and radiation, which can be long-lasting. • The adverse effects of systemic chemotherapy on the central nervous system represent an important toxicity of cancer treatment that can cause multiple adverse neurological effects. These adverse effects are important for multiple chemotherapeutic agents, and across the age spectrum. • In terms of the scope of the problem the therapy would be addressing, while the severity and duration of cancer-related cognitive impairments vary across patient populations and treatments, they affect most people treated for cancer with long-term cognitive decline seen in over 75% of patients. An estimated 15.5 million Americans live with lifelong cognitive deficits resulting from chemobrain, projected to increase to 20.3 million by 2026. Thus the unmet medical need is significant. • The dual attractions for this project are the combination of a relatively recent ultrasound method for addressing a classic issue of localizing stem cell effects to the brain, by permeabilizing the blood brain barrier. The low risk of exosomes versus stem cells, along with the peripheral and non-invasive aspects of this study are relatively novel and mean that there are fewer barriers to ultimate human translation than for other (more common) studies without these properties. • This proposal would increase the likelihood of improving patient care using stem cell technologies, however the use of exosomes themselves is not a bottleneck, as there are 100+ registered clinical trials of exosomes for various conditions. • The major aspects of safety and transitioning from mouse/rat treatment parameters to humans have not been adequately considered. • The proposal addresses an urgent unmet need, but the translational approach is not clear.
No: 2	• The application is missing discussion on scalability, controlling batch to batch variability, and how the proposed therapy might be effective against "chemobrain" effects of different chemotherapy agents.
GWG Votes	**Is the rationale sound?**

Yes: 7	• While the actual molecules in exosomes which are having the therapeutic effect are not nominated beforehand, based on numerous mouse studies and limited human studies, there is high likelihood that the method will have a beneficial cognitive effect.
	• Exosomes have been used successfully in mouse models of brain radiation, epileptic seizure, stroke, traumatic brain injury, and Parkinson's and Alzheimer's disease, all of which support their potential in chemobrain, given the common influence of inflammation.
	• In terms of the rationale for exosomes, cited properties relevant to the project are:
	  ◦ Ease of manufacture and release test procedures.
	  ◦ Ease of transport and storage.
	  ◦ Improved biodistribution via intrevenous cannulation, avoiding the restricted passage of stem cells through the lung capillary.
	  ◦ Improved safety, as exosomes have lower tumorigenicity than stem cells.
	  ◦ Lower immunogenicity, as demonstrated by routine blood transfusions performed with exosomes.
	• The authors have shown preliminary data from their own lab in all the separate components of the study in mice or rats, including that treatment with LIFU increases transfer of exosomes delivered by cannula, and that treatment with exosomes decreases hippocampal inflammation in models of traumatic brain injury.

No: 7	• Rationale is difficult to assess because no experiments were carried out on the topic of the proposal. There are no proof of concept experiments at all in relationship to chemotherapy-induced CNS damage. • No proof of concept data are provided to support the rationale.

	• The application is missing proof of concept studies demonstrating efficacy on chemotherapy-induced brain toxicity. • The understanding of "chemobrain" seems very superficial, and does not address the different kinds of damage, the effects of different chemotherapeutic agents, the problem of multiple toxicities, the contributions of age and gender and genetic background, etc. • The rationale for choosing methotrexate as the insult of choice is not clear. • There is no discussion on the challenges in preparing reagent-grade exosomes in regards to batch-to-batch variation and similar problems. • The rationale suffers without a discussion of addressing batch to batch variability. • The application does not address scaling and CMC for exosomes.
GWG Votes	**Is the project well planned and designed?**
Yes: 7	• Analyses that will be performed to characterize exosomes are not clearly defined.
No: 7	• Fundamentally, this proposal is testing if LIFU (a low intensity well-tolerated ultrasound) will make intravenous exosome delivery in mice more efficacious for treating brain inflammation likely underlying chemobrain. The design is capable of assaying the interaction of LIFU with exosome treatment vs sham, but the question is whether this is a sufficient marker of success to justify continuing to human studies when there is no effort in estimating parameters from this for human application. • No. When there are already hundreds of clinical trials of exosomes in humans for many diseases and LIFU has a strong safety profile, and the researchers are simply proposing intravenous exosomes, it's not clear why there's no human testing. • There is no discussion regarding the problems of scaling and exosome penetration beyond the first cell layer around the vasculature, which is a well studied problem in regards to delivery of virus particles to the central nervous system. • Although there is mention of characterization of exosome contents, there is no information on the nature and interpretation of any analyses to be conducted. • It will be difficult to contextualize RNAseq data from exosomes from the two proposed lines without a comparison to other lines/exosome lacking the proposed benefits. The RNAseq of the mouse brain isn't taking advantage of the spatial transcriptomics results and there's no detailed processing or analysis proposed. Proteomics are only mentioned briefly and there's no detail at all on the very detailed processing necessary for this method. • The spatial transcriptomics usage isn't integrated with other markers, there's no preliminary data on the proposed platform and it appears that this section of the proposal isn't written by someone with hands-on experience with the technology that will be used. While there is some effort to optimize the exosome dosage and LIFU intensity, it would be more impactful to test how these parameters scale up to human application, but this is lacking in the application. • There is extensive characterization of exosomes without any differentiation of efficacy. • The proposal lacks necessary testing of comparable treatment methods. Granted, there are few for chemobrain, but generally recognized means of decreasing brain inflammation such as exercise and a variety of diets could be used as comparisons. • The application mentions comparing NSCs vs exosomes, which would be appropriate, but the experiments listed only include exosome experiments. The exosomes are not compared with NSCs to see if they are as good, better, or less effective, despite the applicant's expertise in the use of NSCs. • It is suggested that NSC-derived exosomes can ameliorate radiation- and chemotherapy-induced cognitive dysfunction by reprogramming impaired neuronal plasticity. Such reprogramming on neuronal plasticity does not appear to be studied. • The effects of LIFU seems to be to increase adhesion and spread in the endothelium, rather than in brain cells. This is not discussed. • In regards to control of inflammation, there is a single figure, not quantified, claiming decreased inflammation in brains of the control aged Wistar rats in response to exosomes. • The application is very preliminary, as there is no discussion on the exosomes actually having efficacy. • The application lacks preliminary studies to demonstrate proof of concept or mechanism for these exosomes.

GWG Votes	Is the project feasible?
Yes: 7	• The outcomes are feasible, but the concern is that they are not analyzed in a way that takes advantage of the assays proposed, there's a lack of comparison methodologies, there are entire assays that are never really described, and there's a lack of experiments that are designed with an eye towards human translation. Thus, while the milestones are achievable, it is questionable whether they are necessary to achieve. • While there is traditional biostatistics expertise on the team, experience in omics analysis is required and the proposal text itself indicates this is lacking.
No: 7	• Problems associated with scaling an exosome therapy are not addressed. • The application is missing key preliminary data. • The project outcomes are not achievable due to a lack of preliminary data. • The applicants are targeting a very variable and heterogenous population and indication, and have not addressed the challenges associated with this in their proposal. • Feasibility is difficult to assess in the absence of proof-of-concept data.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 12	• The applicants plan to conduct studies using male and female mice. There's an argument to be made that the relatively non-invasive aspect of the (eventually/possibly) available treatment might make it more deployable or acceptable to underserved communities.
No: 2	• The application does not account for human diversity in the clinical experience.

Application #	DISC2-15004
Title (as written by the applicant)	A novel cell therapy product that enables engraftment in a minimally invasive site for patients with type 1 diabetes
Research Objective (as written by the applicant)	We develop human stem cell-derived insulin-producing organoids that can be transplanted in a novel site with engraftment enabling factors for improved outcomes in patients.
Impact (as written by the applicant)	Bottlenecks such as availability of cells, loss of graft after surgery, and a challenging transplantation site are addressed in the proposed studies.
Major Proposed Activities (as written by the applicant)	• Define soluble factors that enable stem cell-derived insulin-producing organic engraftment and survival in a novel transplantation site • Optimize delivery method for engraftment factors with the stem cell-derived insulin-producing organoids
Statement of Benefit to California (as written by the applicant)	This safe and effective cell therapy will provide a functional cure for the approximately 3.2 million people living with diabetes in California (approximately 5.7% of which have Type 1 Diabetes). Diagnosed diabetes currently costs an estimated $39.5 billion per year (Sources : ADA and CDC). This one-time cell therapy would significantly reduce the burden of diabetes on the population and reduce the significant health care expense associated with the disease.
Funds Requested	$2,288,000
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: 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	7
Highest	80
Lowest	60
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 13	• The project's candidate is a human cell organoid, primarily comprising pancreatic insulin-producing cells derived from human pluripotent stem cells. The product aims to reverse diabetes and have prolonged function compared to current standards of care. • This is an attractive approach combining the paracrine potential of parathyroid tissue for stem cell-derived insulin producing cells in alternative transplant sites. • The product aims to address unmet medical need in the capability to achieve long-term diabetes reversal after beta cell replacement via transplantation in extrahepatic sites using stem cell-derived islets. • The product combining clinical grade SC-derived islets and biomaterials for local sustained release of factors to favor engraftment in extrahepatic sites remain to be defined, so it's unclear whether it will address these unmet needs. • There is a need to improve stem cell viability with proteins and growth factors. • The proposed experiments will test all aspects of the final product, including the quality of cells generated from stem cells, efficacy of factors for engraftment at a novel transplant site, and disease modification capabilities. The three-pronged approach (cells/factors/site) brings the field closer to changing how islet cell replacement therapy will be carried out in the future. • The research plan focuses on aspects of reproducibility, safety, and assessments of activity for the combined product. Efforts outlined in the proposal will inform the final product, including clinically relevant cells for allogeneic cell replacement therapy.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 9	• Preliminary data are included, but the identification of critical parathyroid-generated factors is under development. • The project's rationale is based on the development of a human cell organoid that will be derived from precise, directed differentiation of a clinically compatible human pluripotent stem cell line. The rationale includes the use of the applicant's proprietary protocol and the combination of defined factors and hydrogel complex with the cells to reverse diabetes.
No: 4	• Preliminary data are needed on the efficacy and maturity of the cells. Even though cells express C peptide, this does not mean that they are good quality mature beta cells. • Preliminary data do not show diabetes reversal after transplantation in immunodeficient mice, even with research grade cells. • Preliminary data with one biomaterial and parathyroid factors at a novel site do not show diabetes reversal. • Data were not provided to support the utilization of the many different biomaterials to provide sustained release of the identified parathyroid growth factors. • There is insufficient preliminary data to support the utilization of the proposed biomaterials to provide local sustained release of identified parathyroid factors. • There is weak rationale for the utilization of biomaterials in the order described without prior optimization of fabrication and biochemical factor release. • The critical factors to be released by biomaterials to provide the same beneficial effects of parathyroid gland co-transplant are unknown. • The application does not address potential challenges moving this therapy into the clinic. • The path to commercialization for this product is not well defined.
GWG Votes	**Is the project well planned and designed?**
Yes: 6	• The project is well planned, with a focus on generating high-quality cells that are safe and effective, identifying the minimal combination of factors that promote cell survival in vivo, and establishing engraftment in a site with easier access. • The project appears to be well-constructed, with a clear focus on how islet cell replacement therapy will be carried out in the future. • The team has not yet convincingly demonstrated the ability to differentiate multiple hPSC lines into beta cells. • Pitfalls are not sufficiently addressed.
No: 7	• This is a very ambitious proposal based on minimal preliminary data.

	• There is a lack of expertise in biomaterials for drug release on the team, and it is concerning that many formulations are proposed without sufficient preliminary data. • The team lacks expertise on hydrogel/biomaterials and drug delivery. • The applicants state that diabetes reversal is a key readout and is one of their milestones, but without any preliminary data showing diabetes reversal after SC-islet transplantation the feasibility of meeting the milestones is low. • The proposed combination therapeutic consisting of drug and polymer has challenges from drug development and scalability perspectives that the applicants have not adequately addressed.
GWG Votes	**Is the project feasible?**
Yes: 8	• The proposal includes testing the functional competence of organoids in small animal models, and this reflects a feasible plan. • A beta cell differentiation expert may be needed.
No: 5	• It is not clear whether the team has the required expertise to support feasibility. • The team and collaborators are well qualified but the proposal is ambitious and unlikely to be achieved. • The delivery of the biological factors and growth factors could present CMC and commercial challenges and expenses.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 13	• Diabetes is largely a patient-managed disease, and studies have shown that health literacy, or the patient's ability to read and comprehend medical instructions, has a strong correlation with glycemic control. Underserved communities may suffer disproportionately from diabetic complications, further reducing their quality of life and increasing the burden on the healthcare infrastructure. • The project outcomes aim to reverse diabetes with prolonged function compared to current standards of care. The product's biological activity includes the release of insulin in response to elevated glucose levels, achieving normoglycemia and independence from daily insulin dosing, serving the unmet medical needs of the population. • The applicants claim they will include iPS cell lines that are generated from women, people of color, and people with diverse ethnic and genetic backgrounds. Several such lines are available on the CIRM repository. • Plans to incorporate patient perspectives and experiences are not discussed.
No: 0	*none*

Application #	DISC2-15009
Title (as written by the applicant)	Reprogramming Autologous Brain Tumor-Infiltrating T Cells to a Stem-Like State for Adoptive Cell Therapy (ACT) Using Immune Competent Organoids
Research Objective (as written by the applicant)	We will use a mini-brain culture system to select and reprogram glioblastoma patients' own T cells to generate a personalized stem cell-based therapy
Impact (as written by the applicant)	Our product will address the toxicity and insufficient anti-tumor activity of currently tested immunotherapeutic approaches for glioblastoma
Major Proposed Activities (as written by the applicant)	• Identification of reagents and experimental conditions to reprogram the cells of interest • Development of a tissue culture process to generate our stem cell-based product • Demonstration of our stem cell-based product functionality in relevant laboratory in vitro models • Testing of the efficacy and mechanism of action of our stem cell-based product in relevant mouse models • Characterization of our stem cell-based product by sequencing at the single cell level
Statement of Benefit to California (as written by the applicant)	Glioblastoma disproportionately affects the elderly. Seniors face unique challenges in accessing health care and are actively excluded from most clinical trials, calling into question the relevance of treatments tested on younger populations. Our proposed product, generated and tested using the patient's own cells, would provide seniors a one-time, personalized treatment. This treatment could translate to other CA patient populations with language barriers, cultural hesitancy, or low means.
Funds Requested	$1,887,752
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	4
Highest	78
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 project hold the necessary significance and potential for impact?
Yes: 10	• The applicant proposes to further develop and test their method for ex-vivo generation of large numbers of autologous tumor-infiltrating lymphocytes (TILs) using glioblastoma organoids. The product will be a therapeutic against glioblastoma, the most common and deadly type of brain tumor. • The applicant proposes use of a novel process to generate the TILs. This process has the potential to generate large numbers of TILs while preserving the original antigen specificity, including tumor-specific specificity. • The TILs in the product will also be reprogrammed into T memory stem cells (TSCM). The stem cell-like properties of the product would include improved lifespan, self-renewal capacity, and effector differentiation potential - potentially generating a product with augmented anti-tumor activity. • Systemically administered tumor infiltrating lymphocytes (TILs) have demonstrated encouraging activity against brain tumors in early clinical trials. As tumor organoids preserve TIL populations without artificial reconstitution, and the cytokines used are known to promote the stem cell phenotype, it may be possible to generate a cell population that would be more efficacious than existing products. • The organoid technology has been developed and investigated in detail for other tumor types. This project is to develop the proposed TILs in the context of a glioblastoma organoid and evaluate the cells' antitumor efficacy in vitro and in vivo. The applicant has a detailed plan and demonstrated capability for investigating and translating the proposed therapeutic. • The applicant has presented a step-by-step progression: method development, testing in vitro, testing in vivo in murine tumor models, and selection of a candidate technology for IND-enabling studies. • The proposed therapeutic candidate is likely to address the unmet need of glioblastoma patients, especially elderly patients, based on its rationale and convincing preliminary data. • Successful therapies for glioblastoma are lacking. If this approach were to increase the efficacy of T cell based therapies, this could be of significant value in better treating these deadly tumors. • The proposed product could potentially activate antitumor immune responses and eradicate tumor cells in the brain. • If successful, the method could have high translational value for cancer immunotherapy. • Overall, yes, though the product looks like it will take some time to be suitable for scaling for human usage, even if everything works perfectly.
No: 2	*none*
GWG Votes	**Is the rationale sound?**

Yes: 5	• As antigen-specific tumor-infiltrating lymphocytes (TILs) with T memory stem cells (TSCM) phenotypes, this product is likely to persist and stay functional in targeting the heterogenous glioblastoma cells. The proposed therapeutic candidate also has the potential to help a wide range of cancer patients.
	• There are at least two major challenges for this proposal:
	  ◦ Establishing a glioblastoma organoid that mimics an immune tumor microenvironment is known to be complicated and challenging. The applicant has successfully established an organoid using one glioblastoma sample (Figure 1B), but their success rate remains to be investigated.
	  ◦ Glioblastoma is known to be immunosuppressive and have limited lymphocyte infiltration. The applicant has shown the team's capability to isolate and expand TILs from other tumor types (in Figure 2), but they may not see similar success with glioblastoma.

No: 7	• The project has a good rationale for preserving tumor specificity in a TIL product using a novel process. The scientific premise for reprogramming TILs into TSCMs is less convincing. The idea is based on the method described in reference 20, but there is a major difference in the starting material. In the reference, the cells were activated for just

	a few days before reprogramming. Here, the TILs are expected to be much more terminally differentiated, and then reprogrammed. • The applicant does not adequately consider or discuss whether a simple organoid system will be an effective model for glioblastoma - a complex tumor that is difficult for cells to infiltrate. • The well-studied immunosuppressive effects of glioblastoma should be considered a potential limitation to this approach. No experiments to examine this are proposed. • This appears to be an early stage proposal lacking data related to glioblastoma. Much of the experiments are related to process development. • Preliminary data do not adequately support the applicant's approach to reprogramming TILs to TSCMs. • This project is relatively early stage, as it lacks preliminary data to suggest tumor cell killing activity. • It appears the tumor cell killing has not yet been assessed.
GWG Votes	**Is the project well planned and designed?**
Yes: 5	• The proposed assays to evaluate the product are relevant. However, a direct experimental comparison between the proposed therapy and currently used therapies is necessary. • The main novelty of this proposal is the reprogramming of TILs to exhibit TSCM phenotypes. The applicant has described the alternative approaches to make this achievable.
No: 7	• The proposal includes a well-developed research plan for generation of TILs and their phenotypic, transcriptional, and functional testing. • The project is critically dependent on the successful TIL to TSCM reprogramming. This should become clear within the first six months. • There is insufficient attention to alternative reprogramming tools that could be tested if the first method is not optimal. • Tumor-specific cytotoxicity is one of the endpoints proposed for measuring therapeutic potential of the reprogramed TILs. Although the assay itself is of high quality, the proposed interpretation is questionable. It's known that TSCM are less cytotoxic, but can provide more durable tumor control in vivo because they maintain themselves and give rise to more cytotoxic progenies. Therefore, in vitro cytotoxicity may be misleading. • The proposal does not include functional assessment of TSCM stemness. • The proposed experimental comparisons are not adequate.
GWG Votes	**Is the project feasible?**
Yes: 8	• The proposed milestones and expected project outcome are logical. • The applicant team is well qualified for the proposed study. • The team has access to all the necessary resources. • The budget is appropriate. • Possibly, but the requisite expertise to show efficacy using organoids is not clearly shown. • The team is well capable of the work, with the exception of the animal model studies. • It will be very challenging to successfully use organoids as models of a complex tumor.
No: 4	• Key Personnel bring substantial experience in cutting edge organoid technology, development of antibody therapeutics and bioanalytical assay systems. However, the team may not have the expertise needed for the testing the efficacy of reprogrammed TILs in xenograft mouse models. • The team has extensive experience with organoid models. The team's lack of experience in translating in vitro findings into in vivo setting in mouse tumor models is a concern. • Many critical experiments have not yet been performed. Technically, the applicant seems able to carry out the proposed experiments but they provide no proof-of-principle that the experiments are worth doing. • The evaluation of pitfalls seems simple considering the lack of data on glioblastoma. • This requires additional preliminary data to support feasibility.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 12	• Glioblastoma is more likely to affect older individuals. The distribution among different races and genders is not selective.

	• The project plan and design adequately address and account for the influence of race, ethnicity, sex and gender diversity.
No: 0	*none*

Application #	DISC2-15057
Title (as written by the applicant)	Identifying Drugs to Amplify Neural Recovery in Combination with NSCs After SCI
Research Objective (as written by the applicant)	Identifying (i) transcriptional changes in corticospinal tract neurons associated with rehabilitation and (ii) new drugs that can mimic this pro-regenerative state in combination with grafted H9 spinal cord neural stem cells (H9-scNSCs)
Impact (as written by the applicant)	If successful, our pharmacological strategy can take a rapid path towards human intervention that can lead to greater functional recovery in patients with spinal cord injury.
Major Proposed Activities (as written by the applicant)	• Identifying the rehabilitative corticospinal transcriptome • Bioinformatics analysis and in-silico analysis using Broad Connectivity Map (Cmap) to identify small molecule leads • Test the effects of novel small molecules for axonal growth in adult corticospinal neurons in vitro • Identify pharmacokinetics and pharmacodynamics mechanism of drug action for further in vivo application • Test the effects of novel small molecules identified for enhanced corticospinal tract regeneration in spinal cord lesion sites treated with H9-scNSC grafts • Assess the effect of novel small molecules identified for enhanced of function outcomes using behavioral assay
Statement of Benefit to California (as written by the applicant)	The proposed grant will find a therapeutic approach that can take a rapid path towards human intervention. If successful this small molecule can increase functional recovery in citizens of California State with spinal cord injury.
Funds Requested	$2,255,315
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	3
Highest	70
Lowest	60
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 12	• The proposal addresses spinal cord injury (SCI), a major unmet medical need. • SCI has no good therapies and is a severely debilitating medical condition. • Discovery of key elements of a 'recovery transcriptome' in corticospinal tract (CST) neurons might yield important insights for drug discovery. Three aims progress from basic research to drug candidate to in vivo assessment. • Extending the window for cell transplantation approaches in spinal cord injury (SCI) is of high clinical relevance. • Partially so. There is definitely an unmet need in SCI, and cell therapy is being explored. The current proposal aims to increase the efficacy of such therapies or increase the therapeutic window. • The small molecule drug(s), if identified and validated, is to be combined with a cell therapy currently in development. • If there is subpar clinical benefit from stem cell therapies this type of approach can be implemented to find small molecule drugs that can enhance the therapeutic benefit of the transplanted cell. It is currently unclear if this is needed.
No: 2	*none*
GWG Votes	**Is the rationale sound?**
Yes: 9	• Yes, the idea to increase the therapeutic window and/or enhance the efficacy of cell therapy in SCI is well-motivated and justified. • Theoretically yes, but in prior work neural stem cell (NSC) transplantation does not appear to drive improvement in SCI. This is shown in the cited publication, where functional outcomes in the rehabilitation-only groups were not different from the transplant-plus-rehabilitation group. • There might be value in bridging the time when a patient is not yet stable enough to engage in rehabilitation therapy. However, no preliminary data are provided to suggest that factors enhancing neurite outgrowth during this time would have benefit. • The applicant's preliminary data support feasibility of the experimental methodology. However, the data do not support the rationale for using a mouse undergoing SCI rehabilitation as a tool to discover small molecules drugs. • The applicant may be assuming that neuronal changes are central to the positive impact of rehabilitation. There is no rationale nor data provided to substantiate this assumption. • Plans for selection of top therapeutic candidates are not described.
No: 5	• Characterization of the 'rehabilitation transcriptome' is justified; the rationale for using NSC grafts in this SCI model to discover drugs could be stronger. • Preliminary data do not show that NSC therapy enhances or improves rehabilitation in this model. • Preliminary data (e.g., Figure 3) do not demonstrate that NSC grafts are effective.
GWG Votes	**Is the project well planned and designed?**
Yes: 6	• The project is well planned and designed. However, plans to merge this product's development with the H9-NSC based grafting approach currently in clinical development for SCI are not clearly mapped out. • Overall, yes, though there is some lack of clarity in group size, timepoints for analyses, etc. • Potential pitfalls are identified and alternative approaches are presented, to a partial extent. • Yes, though there is a risk that no therapeutic candidates will be identified.
No: 8	• Aim 1 is based on the interesting idea that rehabilitation generates or expands the same pro-regenerative state in corticospinal tract (CST) neurons that occurs during injury. During injury, CST neurons regress for a short time to an embryonic transcriptional signature. • Combining rehabilitation with NSC transplantation is not well-rationalized, as the combination is not more effective than rehabilitation alone (Figure 3 and the cited

	publication). This lack of additional benefit suggests that increased neurite extension into grafts does not translate to additional recovery. It is thus not clear why the applicant uses neurite extension and neuronal survival as a relevant readout.
	• The transcriptomic changes to be analyzed in Aim 1 are a readout of treatment with rehabilitation only (Aim 1 has no NSC-graft cohort). The applicant makes the case that these transcriptomic changes will also be relevant to neurite extension into grafts, which is not a valid assumption.
	• Aim 1 is well-designed and will yield important information. However, it's not clear how the project will proceed beyond Aim 1 if the in silico studies do not yield a candidate drug. Also, it's possible that an identified candidate small molecule may act on the graft rather than endogenous CST neurons, making it difficult to interpret the data from Aim 3.
	• Aim 3 has several problems:
	  ◦ It lacks the critical control of SCI plus rehabilitation.
	  ◦ It does not directly test whether drugs extend the pro-regenerative window (time points are not clear).
	  ◦ It does not describe how the applicant will identify or develop small molecule therapies.
	  ◦ There are no clear go/no-go steps for drug development.
	• The reliance on rodent cells for the project may be a weakness.
	• The applicability of the Broad Connectivity Map to this problem is not argued well.

GWG Votes	**Is the project feasible?**
Yes: 6	• The project is feasible, provided that lead candidates are identified. • Yes, the proposed team is appropriately qualified and staffed. • Yes, the team has access to all the necessary resources to conduct the proposed activities. • Yes, the budget is appropriate for the research proposed. • Figure 5 shows transcriptional changes of corticospinal neurons in trained and untrained healthy mice, supporting the feasibility of Aim 1. • Figure 6 shows the ability of the applicant to successfully label CST neurons, and RNAseq analysis of mRNA pulled down shows enrichment for neuronal genes. • Aim 2 depends on using mature neurons to map neurite outgrowth and survival. The applicant proposes to use cortical neurons, while Aim 1 is focused on CST neurons. • The readout in Aim 2 is not clear. In preliminary work, NSC grafts promoted increased neurite outgrowth below the lesion but this was not associated with significant functional improvement. Thus the pro-regenerative transcriptomic profile associated with rehabilitation may not be associated with increased neurite outgrowth. • It is problematic that the applicant is testing the transcriptomic profile in the absence of the NSC graft, but evaluating neurite outgrowth in the presence of the NSC graft.
No: 8	• The preliminary data are not supportive of the proposal. • One study outcome, outgrowth and survival, will not result in a sufficient scientific advance. • Expertise may be limiting. Is the team qualified to create the proposed model? • Feasibility is not clear, because there is no fallback position if the search for candidate drugs in Aim 1 fails.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 13	• The applicant argues rightly that high quality medical care after SCI is not equitably accessible to all patient groups. Unfortunately, as the approach is based on providing a drug to be administered with a stem cell therapy, patients would still rely on access to an expensive SCI program. • The project has potential to inform the development of a product that serves the unmet medical needs of the diverse California population. • The applicant does not clearly describe plans to incorporate perspectives and experience from the population that will benefit from the proposed product in the implementation of the research project. • The applicant explains why they will only use female mice.
No: 1	• The DEI plan is inadequate. The applicant mentions only that African Americans suffer more from SCI than other groups, and includes a vague statement about institutional

	commitment to DEI. The application does not include any indication of PI engagement in DEI.

Application #	DISC2-15174
Title (as written by the applicant)	Immunotherapy for glioblastoma utilizing glioblastoma-targeted microglia derived from human induced pluripotent stem cells (GBT-hiPSC-MG)
Research Objective (as written by the applicant)	Glioblastoma (GB) is an incurable brain cancer. We will derive stem cells from GB patients and bioengineer them to seek out and destroy tumor cells. It is a new strategy to treat brain cancer.
Impact (as written by the applicant)	Glioblastoma and other brain tumors kill ~19,000 people per year in the USA, and nearly 200,000 people per year world-wide. If successful, our therapeutic strategy will save thousands of lives.
Major Proposed Activities (as written by the applicant)	• Derive stem cells ("human induced pluripotent stem cells", or hiPSCs) from blood cells obtained from patients with glioblastoma. • Differentiate the stem cells to microglia (hiPSC-MG), a cell type that protects the brain from infection. The hiPSC-MG will be bioengineered to create GB-targeted microglia (GBT-hiPSC-MG). • Test GBT-hiPSC-MG for efficacy at seeking out and killing GB-tumor cells in vitro, using "Brain-in-a-dish" cocultures of neurons, GBT-hiPSC-MG, and tumor cells. • This project will develop and test GBT-hiPSC-MG in culture dishes, only. If successful, later projects will test GBT-hiPSC-MG in animal models of brain cancer and then in human clinical trials.
Statement of Benefit to California (as written by the applicant)	Our research will initiate development of a novel therapeutic strategy for the treatment of glioblastoma, the most common type of fatal brain cancer. If successful, the new therapeutic strategy will save the lives of people that would otherwise be killed by this disease. The overall incidence rate of glioblastoma is about 2.5 per 100,000 people/year. Since California has about 40 million people, our therapeutic strategy will be applicable to about 1000 people/year in California.
Funds Requested	$1,820,984
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: 45

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

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

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 8	• Targeting glial cells is rational, and there is a large unmet need in glioblastoma.
No: 6	• Glioblastoma multiforme (GBM) is the most common and deadly brain tumor. Development of new immunotherapy for GBM is important. • The proposed use of iPSC-derived microglial cell (hiPSC-MG) as a CAR carrier could offer an alternative to current CAR-T, CAR-NK, and CAR-M (macrophages) that are at various levels of clinical testing in solid tumors including GBM. • However, it has not been made clear why CAR-MG are expected to work better than CAR-M. Considering a much more complex manufacturing for CAR-MG from iPSC compared to CAR-M from peripheral blood monocytes, an advantage of hiPSC-MG should be justified. • While the proposal is in its early stages and primarily focuses on GBT-hiPSC-MG generation, it lacks a comprehensive exploration of cell characterization, therapeutic efficacy, and translational prospects. These aspects warrant a more thorough investigation. • Although the concept is novel, the proposal falls short in terms of scientific rigor and robustness. • Based on the preliminary data, discussed below, it is not clear this work will have any impact. • The significance and potential for impact are lacking, and the project requires more preliminary data.
GWG Votes	**Is the rationale sound?**
Yes: 6	• The recent emphasis on microglia as a target for brain tumor therapies is well-founded due to their strategic positioning and function in the tumor microenvironment. Repurposing CAR technology to leverage microglial phagocytosis for cancer cell elimination is a compelling avenue with considerable potential. • The theoretical rationale for using CAR-MG vs. CAR-T is that the former may better localize to the tumor site, infiltrate tumor mass, and activate phagocytosis. • The practicality of using hiPSC-MG for testing the microglia targeting proteins, in contrast to limited alternatives like murine BV-2 cells or post-mortem human brain-derived microglia, adds credibility to the approach. • The proposed properties of CAR-MG are similar to those observed in CAR-M. It would be important to compare CAR-MG with CAR-M in simple in vitro cytotoxicity/phagocytosis tests to establish a premise for the project. • Considering that applicants have already generated iPSC-derived MG and have patient-derived GBM cells as well as cell lines, it would make sense to perform initial experiments by transducing mature MG with a CAR and testing them against tumor cells. This can be done with CAR-T and CAR-M cells. Such experiments would not take more than 4-6 weeks to obtain a critical go/no go decision for the rest of the project. • The preliminary data demonstrates the capability of the team to generate hiPSC-MG and evaluate them in vitro. However, the absence of preliminary data on the approach's efficacy is a notable gap. • The applicants present an interesting idea, but the concept is very preliminary and the data do not support the idea. • The preliminary data are not sufficient to justify the proposed study. • There is a concern regarding CAR design. A CAR construct that works in T cells may or may not work in MG, so a negative result with such CAR-MG could be misleading.
No: 8	• The project is based on combining two approaches. The first of these is the generation of microglia from hiPSCs, and the second is to express targeting proteins. These are similar in design and function to chimeric antigen receptors. • The hope is that the modified microglia will be able to efficiently engulf and kill glioblastoma tumor cells in vitro. However, this mechanism is not yet supported by the preliminary data:

	● In initial experiments in which GFP- positive clear GB spheroids were grown amongst hiPSC- generated neurons, the applicants report that MG distributed throughout the neurons, and, to a certain extent, to the periphery of the tumor spheroids. In other words, even in this highly favorable situation, they did not observe penetration. The applicants further report that they have not yet observed phagocytosis of the GB tumor cells by the hiPSC-MG. ● The applicants do not address whether microglia engulf neurons. ● The preliminary data are limited, and what is provided is not supportive of the project. ● The study is limited to in vitro assays, no in vivo milestones are proposed.
GWG Votes	**Is the project well planned and designed?**
Yes: 3	● The project is in early stages with limited preliminary data, and the translation to the clinic is not defined.
No: 11	● A number of pitfalls have been acknowledged and addressed, but some concerns remain. For example, the proposed alternative to the lentiviral vector may not be suitable for this study. This vector was used in a referenced study to express a CAR in macrophages. However, this approach may not work in iPSC-derived cells undergoing much more extensive proliferation than mature macrophages. Since the alternate vector does not integrate into genome, expression will likely be lost in MG. ● The project plan, while adequate for proof-of-concept manufacturing, could benefit from heightened ambition. More in-depth exploration of molecular targets, optimization, efficacy testing, and translational considerations is necessary. The proposed candidate's advancement to translation necessitates significant additional work. ● While certain pitfalls are acknowledged, the project's design lacks a translational focus. Particularly, the urgency of treatment for a disease like GBM is not sufficiently addressed. Although the project recognizes the current incompatibility of iPSC-derived therapy production with patient translation, it falls short of suggesting alternative strategies. ● The project's structure could be enhanced. While focusing on iPSC-MG and patient-derived cells is commendable, it's essential to simultaneously conduct efficacy studies using model cells, such as the mentioned THP-1-derived macrophages and established GBM cell lines. This would allow a screen of candidates, and preliminary in vitro and in vivo efficacy evaluations. ● Overall, the experimental plan is logical. However, the entire project is limited to in vitro models. It's still not possible to achieve a proof-of-concept level results for a cell therapy product without in vivo testing. ● The plan suffers from a lack of proposed in vivo studies. ● Critical studies, including in vivo studies, are missing, and negative results were not adequately discussed. ● Although the project is well planned, the lack of attention to the failed preliminary experiments suggests defects in design. ● The project design lacks clarity and detail.
GWG Votes	**Is the project feasible?**
Yes: 5	● The team's publication record demonstrates suitability for the project's execution. The collaboration between the applicant organization and a California-based, well-recognized cancer center network ensures access to comprehensive facilities and instruments for project execution. ● The team is experienced in iPSC, brain tumor research, and functional assays proposed in this study. However, it would help to add an expert in CAR engineering and testing. ● The team has access to many resources required for the study. However, the lack of resources to conduct animal experiments is a major limitation. ● The proposed milestones will likely be achieved within the proposed timeline, but the impact of this study is limited due to the lack of an in vivo model. ● The proposed milestones and expected project outcomes are logical and achievable in the provided timeline. However, it's important to note that the timeline does offer flexibility for potential additional studies beyond the initial focus on cell manufacturing. ● The budget is appropriate. ● Microglia seem not to penetrate the tumor spheres and phagocytosis has not been observed, which limits the validity and feasibility of the overall approach.

No: 9	• There is a lack of preliminary data to support feasibility. • The application lacks key preliminary data to indicate likelihood of success. • Based on the preliminary data, this might be technically feasible but does not yet seem to be biologically feasible in terms of desired endpoints. • Concerns about the CAR approaches suggest that this project may not be feasible.
GWG Votes	**Does the project uphold the principles of diversity, equity and inclusion (DEI)?**
Yes: 14	• The project plan and design adequately address and account for the influence of race, ethnicity, sex and gender diversity. • Much of the consideration of DEI seems to fall on the collaborating cancer center, which is a partner with an excellent DEI track record.
No: 0	• Although the project's scope doesn't explicitly address underserved communities, the potential benefits for the entire population, including those communities, could be significant.