APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Previous CIRM Funding	Disease Indication	Product Type	Approach
DISC2-12577	AAV9-Cas13 gene therapy for Angelman syndrome	**$1,364,903**	**Y**	**91**	91	6	70	95	13	1	N	Angelman syndrome	Gene therapy	Develop a gene therapy that restores expression of UBE3A via antisense RNA expression in neurons
DISC2-12400	Stem cell-derived extracellular vesicles to reverse radiation-induced brain injury	**$1,064,724**	**Y**	**90**	91	2	88	95	13	0	Y	Radiation-induced brain injury	Biologic	Study of neural stem cell-derived vesicles to mitigate radiation-induced damage to the brain
DISC2-12590	A universally applicable skin sheet for Dystrophic Epidermolysis Bullosa via next-generation gene editing, iPS cell technology and tissue engineering	**$1,420,200**	**Y**	**90**	91	4	84	98	13	1	Y	Dystrophic Epidermolysis Bullosa	Cell & gene therapy	Development of a univeral gene correction approach to broaden applicability of an iPSC cell therapy
DISC2-12657	Human iPSC-derived chimeric antigen receptor expressing macrophages for improved cancer treatment.	**$1,414,917**	**Y**	**90**	91	4	85	95	13	0	Y	Ovarian cancer	Cell therapy	Develop a CAR-expressing iPSC-derived macrophage therapy for cancer treatment
DISC2-12666	Development of a new therapeutic for directing target specific stem cell migration and treatment	**$1,129,512**	**Y**	**90**	90	1	90	92	15	0	Y	ALS	Cell therapy & small molecule	Development of a combination therapy of neural stem cells and small molecule to treat ALS
DISC2-12540	Hypoxia-specific Production of Exosomes from iPSC-derivatives for Myocardial Repair	**$1,418,023**	**Y**	**90**	89	2	85	90	15	0	Y	Heart failure	Biologic	Development of an exosome therapy from iPSC-derived cardiomyocytes with miRNA cargo to treat heart failure
DISC2-12669	A novel hybrid CRISPR tool for gene network perturbation and hiPSC engineering	**$705,733**	**Y**	**90**	88	4	79	95	12	3	N	N/A	Research tool	Develop a CRISPR based tool that will allow up and down regulation of multiple genes in iPSC
DISC2-12342	Targeting Critical Regulators of Cancer Stem Cells	**$1,257,814**	**Y**	**88**	88	2	85	90	15	0	N	AML & pancreatic cancer	Small molecule	Identification of a small molecule inhibitor of cell growth & progression signal in cancer stem cells
DISC2-12475	Small Molecules to inhibit Nemo-like Kinase for Treatment of Diamond Blackfan Anemia	**$848,098**	**Y**	**85**	86	1	85	88	15	0	N	Diamond Blackfan Anemia	Small molecule	Identification of small molecule that inhibits Nemo-like kinase and improves erythropoiesis
DISC2-12263	Building a hiPSC-based biopacemaker	**$1,414,113**	**Y**	**85**	85	6	75	90	9	5	Y	Sinoatrial node dysfunction	Cell therapy	Develop a biopacemaker by bioprinting hiPSC-derived cardiomyocytes and fibroblasts
DISC2-12694	Preclinical development of an exhaustion-resistant CAR-T stem cell for cancer immunotherapy	**$1,421,223**	**N**	**84**	83	2	80	87	6*	8	N			
DISC2-12714	Developing Cures for Alpha Thalassemia Using Gene Therapy	**$1,063,386**	**N**	**80**	81	2	80	85	2	13	Y			
DISC2-12499	Developing a common therapeutic for Parkinson's disease and Friedreich's Ataxia	**$1,421,280**	**N**	**80**	81	1	80	85	1	14	Y			
DISC2-12532	Modulation of oral epithelium stem cells by RSpo1 for the prevention of oral mucositis	**$942,050**	**N**	**80**	80	6	70	90	4	10	N			
DISC2-12612	New noncoding RNA chemical entity for heart failure with preserved ejection fraction	**$1,397,412**	**N**	**80**	80	3	75	85	2	13	Y			
DISC2-12255	Glial-restricted progenitor cells and a gene therapy approach for Rett syndrome	**$900,000**	**N**	**80**	80	3	75	84	0	14	Y			
DISC2-12370	An hematopoietic stem-cell-based approach to treat HIV employing CAR T cells and anti-HIV broadly neutralizing antibodies	**$1,143,600**	**N**	**80**	80	1	80	84	0	15	N			
DISC2-12580	Key Tools for Spermatogonial Stem Cell Therapy	**$780,180**	**N**	**80**	80	0	80	81	0	14	N			
DISC2-12588	Metabolic targeting of pancreatic cancer stem cells.	**$1,425,600**	**N**	**80**	80	4	70	84	0	15	N			
DISC2-12603	Therapeutic targeting of Glioblastoma Stem Cell survival and self-renewal signaling	**$1,348,874**	**N**	**80**	80	0	80	80	0	15	N			
DISC2-12358	iPSCs as a screening tool to predict risk of nonalcoholic fatty liver disease	**$813,000**	**N**	**80**	79	7	70	90	5*	9	Y			

APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Previous CIRM Funding	Disease Indication	Product Type	Approach
DISC2-12271	Neural stem cell exosome therapy for COVID-19	**$1,141,776**	**N**	**80**	79	5	70	87	3	12	N			
DISC2-12398	A Fluorescence Lifetime Imaging and Cell Microarray System for Metabolic Tracking and Manipulation of Hematopoietic Stem Cells	**$823,312**	**N**	**80**	79	3	75	84	0	15	N			
DISC2-12354	Quantitative & High Throughput Hematopoietic Stem Cell Purification	**$499,414**	**N**	**80**	78	8	60	88	3	12	N			
DISC2-12639	iPSC extracellular vesicles for diabetes therapy	**$1,345,756**	**N**	**80**	78	6	70	90	2	13	N			
DISC2-12708	Development of Improved Stem Cells for Cardiac Cell-Based Therapy	**$1,414,749**	**N**	**80**	78	4	65	80	0	14	N			
DISC2-12610	Meniscal Repair and Regeneration	**$1,619,109**	**N**	**80**	76	7	62	80	0	14	Y			
DISC2-12544	A synergistic stem cell and gene therapy for glaucoma	**$1,353,283**	**N**	**75**	76	1	75	79	0	13	Y			
DISC2-12690	Pro-angiogenic nanotechnology for neural stem cell transplantation after stroke	**$1,444,500**	**N**	**75**	76	2	75	80	0	15	Y			
DISC2-12678	Development of monothiol human thioredoxin-1 (ORP100S) as an inhaled treatment for COVID-19 respiratory disease	**$1,125,940**	**N**	**75**	75	4	70	90	1	14	N			
DISC2-12644	Extending Immune-Evasive Human Islet-Like Organoids (HILOs) Survival and Function as a Cure for T1D	**$1,543,562**	**N**	**75**	75	3	70	80	0	14	Y			
DISC2-12380	A therapeutic antibody to promote macrophage-mediated killing of cancer stem cells	**$1,425,546**	**N**	**75**	73	2	70	75	0	14	Y			
DISC2-12486	A BioMEMS platform for multiplexed, non-viral nuclear delivery of biomolecules into human stem cells using surface-functionalized silicon nanoneedles	**$495,460**	**N**	**75**	73	7	50	80	0	15	N			
DISC2-12312	A human pre-implantation embryo tool to discover mechanisms and therapies for rare genetic diseases	**$590,100**	**N**	**75**	72	8	60	85	1	14	N			
DISC2-12412	Generation of safe beta-like cells from pluripotent stem cells for treating type 1 diabetes	**$1,124,122**	**N**	**70**	71	2	70	75	0	15	N			
DISC2-12654	MitoPunch production of iPSC derivatives as therapeutic candidates for in vivo mitochondrial transfer	**$1,384,586**	**N**	**70**	71	2	70	75	0	15	N			
DISC2-12360	Matrix Assisted Cell Transplantation of Promyogenic Fibroadipogenic Progenitor (FAP) Stem Cells	**$1,221,120**	**N**	**70**	70	1	67	70	0	13	N			
DISC2-12564	Excitatory spinal interneurons from human pluripotent stem cells to treat spinal cord injury	**$1,512,993**	**N**	**70**	70	0	70	70	0	12	Y			
DISC2-12593	AAV-CRISPR Gene Therapy to Silence the Huntingtin Gene in Huntington's disease	**$1,379,619**	**N**	**70**	70	5	60	80	0	15	N			
DISC2-12626	Narrowing the Outcomes Gap: STING-activating iPS-NK cells for the Systemic Treatment of Gynecological Cancers	**$834,000**	**N**	**70**	70	2	65	75	0	15	N			
DISC2-12455	Creation of a human iPSC-derived microfluidic blood brain organoid barrier for pharmacological testing	**$785,390**	**N**	**70**	66	8	50	75	0	15	Y			
DISC2-12583	3D Printed Physiologically Informed Implants for Spinal Cord Injury Repair	**$900,000**	**N**	**65**	68	5	60	80	0	15	N			

APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Previous CIRM Funding	Disease Indication	Product Type	Approach
DISC2-12634	Development of small molecules to restore function in neurons from Intellectual Disability Syndromes	**$1,383,775**	**N**	**65**	65	1	60	65	0	15	N			
DISC2-12341	Developing Universal Donor Endothelial Cells from Human IPSCs for Revascularization	**$1,410,494**	**N**	**65**	62	9	50	70	0	14	N			
DISC2-12374	Treating advanced retinal degeneration diseases using a tissue engineered co-graft	**$1,290,414**	**N**	**60**	62	4	60	75	0	14	Y			
DISC2-12273	Molecular manual for human hematopoietic stem cell development	**$500,000**	**N**	**60**	61	17	25	85	1	14	Y			
DISC2-12436	Autologous iPSC-Derived T cell Therapy with Diverse TCRs for Non-Small Cell Lung Cancer	**$867,000**	**N**	**60**	60	5	51	70	0	14	N			
DISC2-12637	Stem cell driven regeneration for the treatment of idiopathic pulmonary fibrosis (IPF)	**$1,225,080**	**N**	**60**	60	2	55	65	0	14	N			
DISC2-12301	Characterization and optimization of mutational burden in ex vivo expanded HSC for cell and gene therapies	**$1,151,183**	**N**	**60**	59	5	50	70	0	15	Y			
DISC2-12710	Product Development of Bioprinted iPSC-derived β cell Spheroid Mesh for Treatment of Insulin-dependent Diabetes Mellitus	**$1,083,750**	**N**	**60**	57	5	50	65	0	15	N			
DISC2-12293	Epigenetically stable human Tregs with stem-like properties for graft-vs-host disease	**$1,463,400**	**N**	**-**	-	-	-	-	1	14	N			
DISC2-12397	Intracerebral Neural Stem Cell Transplantation to Treat Mucopolysaccharidosis IIIA	**$1,132,318**	**N**	**-**	-	-	-	-	0	15	N			
DISC2-12535	Development of Stem Cell Therapy for Sanfilippo B	**$1,426,350**	**N**	**-**	-	-	-	-	0	15	N			
DISC2-12422	Targeted correction of autologous iPSC-derived RPE with high-risk AMD variants and evaluation of vision rescue in RPE defective murine models	**$900,000**	**N**	**-**	-	-	-	-	0	12	N			

*** Qualify for Minority Report**

Application #	DISC2-12577
Title (as written by the applicant)	AAV9-Cas13 gene therapy for Angelman syndrome
Research Objective (as written by the applicant)	AAV9-Cas13 gene therapy for Angelman syndrome using a first-in-kind mechanism of action that will safely and permanently restore expression of endogenous UBE3A that is deficient in CNS neurons.
Impact (as written by the applicant)	Angelman syndrome is a rare (1 in 15,000 births) neurogenetic disorder caused by loss of UBE3A in the brain, causing severe developmental delay, ataxia and epilepsy. There are no treatments or cures.
Major Proposed Activities (as written by the applicant)	• Determine the optimal Cas13 guide-RNA for a rodent model. • Determine the optimal Cas13 guide-RNA for a humans. • Show that the gene therapy improves gene expression in rodent models. • Show that the gene therapy improves gene expression in human cells. • Show that the gene therapy improves symptoms in rodent models. • Show that the gene therapy can be safe and permanent.
Statement of Benefit to California (as written by the applicant)	In addition to directly benefiting the ~2,500 children and families living with Angelman syndrome in California, this gene therapy with a first-in-kind mechanism of action could bring new treatments and new opportunities to our state. California has long been a hub of innovation, and creates an environment in which new technologies can be born, fostered, and attract others who want to create a better future for our residents. This activity will help train some of them, and inspire many others.
Funds Requested	$1,364,903
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: 91

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	91
Median	91
Standard Deviation	6
Highest	95
Lowest	70
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	1

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 9	• Angelman syndrome (AS) is a rare (1 in 15,000 births) neurogenetic disorder caused by loss of ubiquitin ligase E3A (UBE3A) gene expression in the brain. There is no treatment for this disease.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 9	• Current clinical trial using antisense oligonucleotide has already shown tolerability and some measures of benefits in treated children. However, the repeated delivery under anesthesia is a significant hurdle to long-term care and there are concerns of off-target effects. The applicants propose a new approach using Cas13, which, unlike Cas9, does not create a double-strand break within the DNA. • AAV9-Cas13 is a gene therapy that will deliver a targetable RNA nuclease to the brain that will cleave the antisense transcript in a region that preserves all normal functions but restores endogenous physiological expression of paternal UBE3A for the lifetime of the individual. • Cas13 good alternative to Cas9 • As the imprinting, and thus the loss of UBE3A expression, only occurs in mature neurons targeting mature neurons would be smart and limit off-target effects. Also development is probably normal. • The proposal is also based on a rat model developed by the applicants who further collaborate with groups developing highly sensitive and clinically meaningful behavioral tests. • The science is sound and also is interesting. The approach is creative, and all steps are thoughtful. • There is a lot of critical supporting data.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 9	• The options for progression are well considered, and much of this work is being developed together with a foundation devoted to development of treatments for this disease. • Well-defined aims. • In vivo milestones should perhaps be prioritized.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 9	• The project is well planned, and the likelihood of advancing to translation seems reasonable. • Expertise is demonstrated, strong preliminary data. • Although the experiments have been powered to be meaningful statistically, the number of animals suggested is somewhat low.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 9	• The inclusion plan is also well discussed/integrated. • Rare diseases of this nature do not discriminate based on race, ethnicity or other relevant issues. • Use human iPS cells from two different donors to consider donor variation, animal studies are powered to consider sex differences. • Key personnel participates in the CIRM-sponsored Bridges program, which offers research opportunities to students from local collages with diverse backgrounds, circumstances and opportunities.
No: 0	*none*

Application #	DISC2-12400
Title (as written by the applicant)	Stem cell-derived extracellular vesicles to reverse radiation-induced brain injury
Research Objective (as written by the applicant)	These preclinical studies will discover the efficacy of stem cell-derived, nanoscale, extracellular vesicles (candidate) to treat adverse effects of cancer therapy on brain function and cognition.
Impact (as written by the applicant)	Stem cell-derived extracellular vesicles will address the confounders of stem cells (tumors, immunorejection, immunosuppression) & mitigate debilitating side-effects of cancer therapy on the brain.
Major Proposed Activities (as written by the applicant)	• Demonstrate the effectiveness of IV injections of stem cell-derived, nanoscale, extracellular-vesicles (EVs) to improve cognition in the mouse model of radiation- and chemo-therapy for brain cancers. • Determine the ability of EV treatment to protect against adverse effects of cancer therapy including neuro-inflammation, synaptic and micro-vascular damage in the brain. • Establish the neurocognitive benefits of injecting stem cell-derived-EV in brain cancer-bearing mice receiving combined radiation- and temozolomide chemo-therapy (CRT-TMZ). • Elucidate the impact of stem cell-derived-EV injections on neuropathological hallmarks of radiation- and chemo-therapy (TMZ) in the cancer-bearing mice brains. • Determine the safety and rule out the toxicity of stem cell-derived EV treatment in brain and peripheral organs in the mice receiving radiation- and chemo-therapy (TMZ) for brain cancer. • Confirm miRNA-124-based mechanism (commonly found within the EV cargo) of stem cell-derived EV-mediated neuroprotection in the mice undergoing radiation- and chemo-therapy for brain cancers.
Statement of Benefit to California (as written by the applicant)	In California, nearly 187,000 patients diagnosed with cancer will be alive in 5 years & more than 1.88 million have a history of cancer. Importantly, adult & childhood cancer survivors suffer from severe & persistent cognitive deficits that adversely affect their quality of life (QOL). A stem cell-based therapeutic could reduce inflammation & restore the cognitive function that may significantly improve patient's QOL, reduce financial hardship on patients, caregivers & the state of California.
Funds Requested	$1,064,724
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	91
Median	90
Standard Deviation	2

Highest	95
Lowest	88
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 11	• The unmet medical need is clearly established in the introduction. The authors outline the prevalence of cognitive impairments as a result of cancer therapy. Currently, there are no available therapies to address this unintended consequence of cancer treatment. This need is particularly high after cancer treatment in children and patients with brain tumours, although many cancer patients will experience cognitive decline after treatment and would therefore benefit from this approach. • The applicant is pursuing two different approaches to the important problem of decreasing cognitive impairment after cranial radiotherapy and adjuvant chemotherapy. One of them, the use of extracellular vesicles, is scientifically interesting and provides the basis for an approach based on delivering a micro RNA (miR-124) that may be better suited for clinical development. • The possibility of preventing and reversing cognitive damage associated with radiation to the brain is an important one, and the demonstration that this is possible, particularly with a therapy that can be delivered through the vasculature, will greatly help to promote research in this field. • Childhood survivors of brain cancers can show reductions in I.Q. of up to 3 points. No clinical recourse is available yet to address this issue. Survivors of pediatric brain cancer and low-grade glioma (LGG) patients often have low quality of life.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 11	• The investigators have presented sound scientific rationale for the proposed project. They have described both the cognitive deficits observed in cancer survivors as well as provided information on the potential mechanisms driving these changes. They have additionally offered pre-clinical evidence that their proposed therapy can modify the underlying causes of cognitive decline in this patient group. • The rationale for this proposal has developed out of sound scientific experimentation that began with cell transplantation with neuroepithelial stem cells. The use of extracellular vesicles is a logical development from this beginning, and the progression to identification of a single micro RNA species that is part of the cargo of the extracellular vesicles is another promising step forward. • The EV-derived candidate miRNA-based mechanism they identified to ameliorate clinically relevant brain cancer therapy-induced cognitive impairments and neuroinflammation adds a layer of novel mechanism.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**

Yes:
11
	• The provided preliminary data supports the feasibility of the proposed EV treatment in rats. It demonstrates that the team possesses the technical knowledge required to set up the glioma model, perform treatments and evaluate behavior and histopathology post-treatment.
	• The preliminary data are quite striking in demonstrating the ability of the extracellular vesicles to treat cognitive impairments and irradiated animals.
	• The ability to treat immunocompetent animals through a relatively noninvasive injection is a very surprising outcome that is also quite promising.
	• Strong preliminary data.
	• The applicant provides extensive preliminary data demonstrating their ability to produce hNSC-derived EVs. However, there is little information detailing how EV quality and homogeneity of EV cargo will be evaluated between batches. In addition, the investigator proposed to utilize EVs in the exosome size-range (40-100 nm) but no details are provided regarding how this particular EV population will be isolated after ultracentrifugation nor why it is specifically targeted.
	• A number of potential pitfalls identified by the applicant have been thoroughly addressed for each aim proposed. The applicants have clearly delineated the main limitations of their studies and suggested adequate alternatives. However, other important pitfalls and alternatives have not been identified and/or discussed:
	  ◦ It is well recognized that stem cell-based models frequently suffer from variability between cell passages. While the applicants describe a verification step for EV size, other factors such as expression levels of bioactive miRNA(s) and marker proteins would also be important to evaluate between batches. To this end, what are the criteria used to define a therapeutic EV? Is it based on miRNA composition?
	  ◦ In Aim 3, the applicant proposes an AAV approach to evaluate the neuroprotective potential of the miRNA. While this is an important aspect for validating the hNSC-derived EV therapeutic potential, the proposed experiment should include additional endpoint measures. For example, what will be the levels of the miRNA expression and how does it compare to EV-based cargo delivery? It seems unlikely that an overexpression model accurately recapitulates the miRNA levels from EV delivery. In addition, it is unclear which cell types uptake hNSC-derived EVs, thus proposing a broad AAV-based delivery may not mimic the EV mechanism of action.
	  ◦ The proposed experimental timeline indicates that EV injections will begin after CRT-TMZ treatment has already induced neuronal damage. Parallel experiments where EVs are injected as a pre-treatment to prevent neuronal damage could also be considered. This approach could be more beneficial for patients by directly preventing neuronal loss and neuroinflammation, instead of rescuing or attempting to regenerate cells after damage.
	  ◦ To understand the molecular effects of hNSC-derived EV treatment, the study could benefit from a single cell RNA-seq experiment to evaluate the response of individual cell types to EV injections (in healthy animals and after CRT-TMZ treatment).
	  ◦ It is unclear whether fibroblast-derived EVs are appropriate controls for this experiment. These EVs are likely to contain bioactive cargo which may trigger a detrimental response.
	• Overexpression of a miRNA could be problematic as miRNA have thousands of targets.

No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 11	• The applicant described multiple different milestones relating both to behavioral phenotypes and to the assessment of inflammation and blood-brain barrier integrity. While the proposed work is substantial, the short duration of the experiments and the specificity of the post-mortem plan should facilitate completion within the stated timeline.

	• The options for progression are thoughtful in two ways. First, the ability to deliver extracellular vesicles via the vasculature and have beneficial effects is much more realistic than cell transplantation. Second, the ability to focus attention on a single micro RNA carried in the extracellular vesicles, which are difficult to develop commercially, provides an interesting option for further development. • The approach uses EV derived from already funded iPSC cells and aims are logical. Progression to EV-derived miRNA to reverse treatment induced cognitive dysfunction is a novel approach.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 11	• The applicants have meticulously described the influence of race, ethnicity, sex and gender on cognitive impairments after cancer treatment. The incidence of cancer has been broken down into specific categories to provide an overview as to how this affects all sub-groups of individuals, in the world and in California as well. • This section of the proposal was extremely well justified. While most of these factors cannot directly be addressed in the current study design, sex has been considered and all experiments include both male and female mice. • There is no doubt that if the applicants are successful in bringing this to the clinic, all cancer patients affected by these major side-effects of chemo and radiation therapy would benefit from their treatment, especially younger patients who are likely to live with these debilitating cognitive affectations for many years. • The proposal mentioned that these detrimental side-effects are more prevalent in certain underserved racial/ethnic communities. While it is unclear where the supporting epidemiological data for this statement comes from, if a cost-effective therapy is produced it is likely to be of significant benefit to this population. However, the route of treatment delivery would have to be re-evaluated for humans but I believe this would be a minor obstacle to clinical translation. • Cognitive problems after cancer treatment do not segregate according to race, ethnicity or related variables. • Well addressed.
No: 0	*none*

Application #	DISC2-12590
Title (as written by the applicant)	A universally applicable skin sheet for Dystrophic Epidermolysis Bullosa via next-generation gene editing, iPS cell technology and tissue engineering
Research Objective (as written by the applicant)	We will develop a cell therapy for a rare skin disease. Patient-derived iPS cells will be genetically corrected and differentiated into epithelial sheets to be grafted on skin wounds.
Impact (as written by the applicant)	In this proposal we will develop a universal genetic correction strategy for all COL7A1 which will be a prerequisite for the commercial viability of our iPS cell-based cell therapy.
Major Proposed Activities (as written by the applicant)	• Replacing a medium size fragment of the COLLAGEN7A1 locus • Excision of the entire COLLAGEN7A1 locus • Replacement of the entire COLLAGEN7A1 locus with a normal copy • Differentiate corrected iPS cells into skin cells • Develop a clinical-grade cell purification system for skin cells • Verify that manufactured skin cells are functional.
Statement of Benefit to California (as written by the applicant)	Our ultimate goal is to bring our iPSC-based therapy into the clinic. Our product will have to be commercially viable to ensure sufficient funding through Phase III clinical testing, FDA approval, and production at scale to provide it to the entire patient community. This therapy will directly benefit Dystrophic Epidermolysis Bullosa (DEB) patients in California. More Californians will benefit from future therapies based on our platform. Finally, academic and commercial development will benefit California's economy.
Funds Requested	$1,420,200
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 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	91
Median	90
Standard Deviation	4
Highest	98
Lowest	84
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	1

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 11	• This third generation approach will be a non-viral universal gene-correction and could be applied to most monogenetic disorders in future. The work has a high chance of success given the strong clinical position to date and could have strong outcomes for both Dystrophic Epidermolysis Bullosa (DEB) patients and for those with other monogenetic diseases. • This is a high risk-high impact proposal. If it works, it will have a broad impact to treat patients with genetic mutations. • DEB still requires an efficacious therapy for a broad range of patients. • The project builds on experience with a first generation cell therapy for DEB, a rare and serious orphan disease. The first generation treatment utilizes engineered, autologous epidermal sheets transfected with retroviral delivery of COl7A1 as a means of correcting the basement membrane dysfunction due to the causative mutation in this collagen gene. • Phase I/II testing of the first generation therapy has been successfully concluded with positive results and now has orphan disease designation in the USA and UK. However, this first generation treatment has limitations because of its autologous derivation and the limited availability of keratinocytes from the patient's wound bed. This does not allow a fully scaled treatment in all cases. • A second generation cell therapy for DEB is based on genetic correction of the COL7A1 locus, derivation of autologous iPSCs and their differentiation to keratinocytes. A new workflow process allows for completion of production of the therapeutic within 3 months of the initial patient biopsy, achieved by combining CRISPR editing and iPSC generation in one step. This treatment has been fully validated in vitro and pre-clinical models are nearly complete, including safety data. However, a recent clarification by the FDA has indicated that the second generation approach will require a new IND for each mutation that is targeted, which would prevent treatment for large numbers of patients. The work will progress to clinical trial for the most common mutation, but a new universal, gene editing approach will be needed to enable all patients to be treated in the future.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 10	• To move from single mutation correction to replacement of whole/partial gene will have a large impact, moving into clinic faster by eliminating some of the limitations of moving gene editing into the clinic. • Yes.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 10	• This set of experimental approaches will lead to the development of a "universal" therapy that will be ready for further clinical development (GMP production and testing in animal models for off-target effects as well as efficacy). • All the proposed experiments are planned and designed. There is some grade of difficulty in the insertion of very large fragments of DNA.
No: 1	• The plan is too ambitious given the preliminary data presented in the proposal. The GMP manufacturing and toxicity of the oligonucleotide donor need to be better considered in the plan.

GWG Votes	Is the proposal feasible?
Yes: 9	• The project is challenging but feasible. • There is some concern in the efficacy of the gene insertion. There is no preliminary data that support their ability to insert the gene. However, the group is highly qualified to work on the methods. • Panel had some concerns about ability to knock in such a large insert. There was a desire for more preliminary data demonstrating proof of the group's capability to do this.
No: 2	• The efficiencies of gene correction are likely too low for manufacturing this product in time and at scale.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 11	• The project addresses DEB which is rare, though one mutation is dominant in the Mexican community. The platform nature of the technology suggests that all communities will benefit from the work in time. • There are mutations in Col7A1 gene that are prevalent in minority populations. • The new strategy would help serve a broader range of projects.
No: 0	*none*

Application #	DISC2-12657
Title (as written by the applicant)	Human iPSC-derived chimeric antigen receptor expressing macrophages for improved cancer treatment
Research Objective (as written by the applicant)	These studies will produce a new CAR-targeted iPSC-derived macrophage-based cell therapy product for treatment of refractory malignancies such as ovarian cancer.
Impact (as written by the applicant)	These studies eliminate a bottleneck in macrophage production and enable these cells to be engineered and manufactured in a standardized, off-the-shelf manner, rather than on a patient-specific basis.
Major Proposed Activities (as written by the applicant)	• Generate of human iPSCs with stable expression of tumor antigen-targeted chimeric antigen receptor constructs • Generate and evaluate in vitro anti-cancer activity of human iPSC-derived CAR-expressing macrophages (human iPSC-CARMAs) with different intracellular signaling modalities • Demonstrate efficacy of human iPSC-CARMAs against ovarian cancer in vivo • Improve efficacy of human iPSC-CARMAs in vitro and in vivo by combination with additional immune stimulating agents agents • Enable large-scale expansion of iPSC-CARMACs via autonomous cytokine expression. • Improved cryopreservation of iPSC-CARMACs
Statement of Benefit to California (as written by the applicant)	Over 2500 women per year in California are diagnosed with ovarian cancer, and the majority of these women will die of their disease. If this cancer is not cured at an early stage, the disease will almost inevitably relapse. Therefore, new and better treatments are desperately needed. This project to use human iPSC-derived macrophages for a targeted cancer treatment provides a completely new strategy for better treatment and cure of ovarian cancer and other refractory malignancies.
Funds Requested	$1,414,917
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	91
Median	90
Standard Deviation	4
Highest	95
Lowest	85
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 10	• The development of novel forms of adoptive immunotherapy may be important. • Overall I do think this work will make research progress toward a potential new, targeted off-the-shelf immune therapy that maybe useful for the treatment of solid tumors. Cell therapies for solid tumors are a clear unmet medical need. • They have identified and will use iPSCs that are suitable for clinical translation and these new DISC2 studies may lead to subsequent CIRM TRAN and/or CLIN grants that, if successful, will translate these CAR-macrophages into clinical trials, potentially to also be combined with NK cells, T cells and/or other immune stimulating agents for new cancer therapies. • New product with potentially broad applications. • They will pilot, for eventual clinical translation, iPSC-CAR macrophages that themselves secrete cytokines and hopefully enable larger-scaled up cell production. • They also propose to define the best way to freeze iPSC-derived CAR macrophages for storage. Cryopreservation is a challenge for cell therapy products and these types of studies although not glamorous will increase the use of these "off the shelf" cells.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 10	• Yes. Adoptive cell therapy for treatment of cancer has become a reality in the last 10 years. Autologous CAR T cells are FDA approved for treatment of B cell malignancies. NK cells have also become of interest in adoptive cell therapies. A big benefit of iPSC derived NK cells is that they function as allogeneic immune cells, so can they can be "off-the-shelf". They will mimic this here for macrophages. • The group has already produced iPSC-derived CAR-expressing NK cells with NK cell-specific signaling domains that showed improved specificity of killing of both hematologic cancer cells (anti-CD19) and solid tumor cells (anti-mesothelin). This strategy and other iPSC-NK cell products have shown activity and safety in early-stage clinical trials. • Even though CAR-T cells and CAR-NK cells are in multiple trials for multiple tumors, the use of these engineered T and NK cells for treatment of solid tumors is not hopeful. This is thought by many to be due to the absence of their cellular infiltration into the more complex solid tumors that are known to also have an immune suppressive tumor microenvironment. It's a rational hypothesis for the mechanism of resistance. • The rationale for use of macrophages is warranted given that they may be the only immune cells in tumors. • The use of additional macrophage stimulating ligands is logical. • It is not clear why other macrophage studies have failed.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 10	• The quality of this project is good and its description is clear. The team should be able to accomplish it in the two year time-span. • They will test a large panel of iPSC-CARMAs for improved killing of ovarian cancer in vitro and in vivo. To increase iPSC-CARMA anti-cancer activity, inhibitors and innate immune modulators will be combined with the iPSC-CARMAs as well. This will increase their chances of having a candidate for translation.

	• There are no concerns with the experimental methods. • Pitfalls and alternatives are described. • The final two tasks make the proposal overambitious. • There is no consideration of macrophage polarization in the studies. • There is little consideration of the immunity raised against the allogeneic cells.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 10	• Yes. The milestones are doable and may be achieved within the proposed timeline. • The PI has decades of experience in hematology and immunology research. The team has contributed to the area where human pluripotent stem cells can be used to produce monocytes/macrophages as in this grant. The team was the first to demonstrate development of HSC from huES cells and from those they could make monocytes. • The postdoc who will spend all of their time on the project developed ways to make iPSC-derived monocytes and showing that they can express novel CARs to hopefully improve anti-tumor activity. • The team for this project is rounded out by a long time research assistant and the longtime lab manager. In addition to work with immune cells they have expertise with mice studies complementing the rest of the team. The lab is focused on studies of blood and immune cell development from human pluripotent stem cells, so their techniques are well established and there will be no learning curve.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 10	• There are no exclusions of gender or ethnicity but they also don't have clinical trials planned here. They do have a diverse training environment. • Yes.
No: 0	*none*

Application #	DISC2-12666
Title (as written by the applicant)	Development of a new therapeutic for directing target specific stem cell migration and treatment
Research Objective (as written by the applicant)	A drug-stem cell combination therapy wherein the drug will direct and promote the delivery and distribution of stem cells to the disease site for the optimal therapeutic effect of the stem cells
Impact (as written by the applicant)	Amyotrophic lateral sclerosis (ALS) and the way to deliver and enhance stem cell-based treatment of ALS
Major Proposed Activities (as written by the applicant)	• Complete the additional in vitro studies and initiate the in vivo studies in SOD1 mouse model • Determine whether the combined effect of hNSCs intraparenchymally augmented/guided by SDV1a has a synergistic effect on improving disease onset/progression & symptom-free survival in the SOD1 mouse • Establish the preliminary toxicity and pharmacokinetics profiles of SDV1a in mouse model • Elucidation of structure and other characteristics; development and validation of analytical procedures • Process development and characterization in lab scale, stability study
Statement of Benefit to California (as written by the applicant)	This new therapeutic will address a significant unmet medical need in the treatment of amyotrophic lateral sclerosis (ALS) and have important benefits to the patients with ALS and impact on the healthcare and bio industry in California.
Funds Requested	$1,129,512
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 90

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

Mean	90
Median	90
Standard Deviation	1
Highest	92
Lowest	90
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	15
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 10	• ALS is a costly and cruel disease with no cure, targeting single processes has not worked. • ALS is a serious disease. The compound to be developed shows promise for ameliorating this disease. • The application is a resubmission with most points addressed. • Stem cells have shown modest efficacy but sufficient dissemination of transplanted stem cells remains a bottleneck. • SDV1a represents the first tool to achieve direct migration & distribution of therapeutic cells to regions in need. SDV1a importantly can direct migration of hNSCs in the brains of normal adult mice without evoking any inflammation. • hNSCs are already in Phase 2 trials for ALS and the applicants drug is expected to get FDA approval and could together have a relatively near-term impact on ALS patients. • However, there are are limited details on a progression plan for FDA approval.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 10	• Yes. The proposal aims to advance SDV1a by testing for off target effects, in-vivo efficacy, dose response, and manufacturing requirements. • NSC efficacy in ALS models correlates directly with the expanse of diseased neuroaxis covered & the degree of chimerism achieved suggesting that migration and chemotaxis is a critical component of any stem cell approach. • Increasing directed migration without inflammation would certainly increase efficacy, thus focusing on further studies of SDV1a as a therapeutic candidate in combination with hNSCs to direct & promote target-specific stem cell migration & treatment for ALS is reasonable.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 10	• The applicants have done an excellent job of addressing the criticisms from the previous review. • Previous concerns about administration have been addressed. • The proposal is basically a repeat of previous work in Sandoff in an ALS model. • Previous published work increases confidence. • The applicant presents pitfalls. • Avoid unnecessary acronyms e.g., routes of administration (ROA).
No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 10	• The milestones are straightforward. • Co-administration of SDV1a with hNSCs was conducted in Sandoff disease and showed promising results.

	• Team is highly qualified and previous CIRM funding led to successful insights that are used in this application.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 10	• This should be a universally applicable drug. • Sex of animals and iPSC cells use is not specified and should have been addressed.
No: 0	*none*

Application #	DISC2-12540
Title (as written by the applicant)	Hypoxia-specific Production of Exosomes from iPSC-derivatives for Myocardial Repair
Research Objective (as written by the applicant)	A lead therapeutic candidate will be selected: 1) exosomes from hypoxia-injured iPSC-derived cardiomyocytes (iCMs), 2) exosomal miRNA cluster, and 3) siRNA inhibition of exosomal target gene, Notch3.
Impact (as written by the applicant)	Effective targeted therapy to restore the injured and vulnerable myocardium is urgently needed to reduce the high mortality of HF patients. Promising discovery of iPSC biology will restore the heart.
Major Proposed Activities (as written by the applicant)	• Patient-specific iCMs are generated from 4 heart failure (HF) patients (2 white and 2 under-represented minority). Exosomes are generated from their hypoxia-injured iCMs to compare their efficacy. • The proliferative and reparative effects of hEx1-4, hEx molecular cargo, miR20b/92a, and hEx molecular target, Notch3, are compared, using hypoxia-injury model of iCMs from a normal subject. • The therapeutic efficacy of the 2 leading hEx determined above, miR20b/92a, and siNotch3 will be compared in porcine HF model. Cardiomyocyte proliferation and myocardial restoration will be confirmed. • A leading candidate will be identified. Dose-dependent myocardial restoration will determine the optimal balance between cardiomyocyte proliferation and electromechanical stability of the heart. • Pre-pre-IND FDA meeting will be held at Month 22.
Statement of Benefit to California (as written by the applicant)	In California, heart failure (HF) is the leading cause of hospital admission and a major public health epidemic. Despite significant therapeutic advances over the last 3 decades, 5-year survival is a dismal 50% today. Furthermore, racial disparity is observed in the care of HF patients. Ischemic injury is the primary etiology of HF. Restoration of the heart by proliferating the cardiomyocytes to repair the injury will transform our therapeutic approach and address a critical unmet need in HF.
Funds Requested	$1,418,023
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 90

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

Mean	89
Median	90
Standard Deviation	2
Highest	90
Lowest	85
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	15

(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 10	• Heart failure affects large numbers of patients worldwide and there remains a poor 5 year survival rate despite advances in conventional therapeutics. A new therapeutic, if effective, would help to reduce the burden of this disease. • The aim is to use exosomes derived from hypoxic cardiac myocytes, or their downstream effectors, to treat myocardial injury. • The proposed work will further investigate the mechanism of myocardial repair by hypoxia-derived exosomes and explore the therapeutic use of exosomes. One of the three therapeutics will be chosen for development as the lead candidate for treatment of heart failure. • Exosomes and exosome-derived molecules have significant potential to improve myocardial repair resulting from ischemia-reperfusion injury by stimulating proliferation of endogenous cardiomyocytes. • miRNAs have particular promise as a therapeutic because of their manufacturability, as compared to exosomes. • Preliminary studies by this team identified that iPSC-cardiomyocyte-derived exosomes stimulate CM proliferation in vitro and in vivo models. Assessment of the exosomes identified miRs that appear to mediate this response. This discovery used stem cells, but the envisioned therapy is likely to be a biologic rather than a stem cell-based therapy. • The proposed work is carefully designed to better understand mechanisms as well as exploring effectiveness and optimal dosing. There is a good chance that a lead candidate will be identified from the proposed work. • The proposal provides a clear path to translation by evaluating the human exosomes and miRs in iPSC-CMs in vitro and in a porcine chronic IR injury model in vivo. These data are a logical path toward clinical translation.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 10	• The use of iPSC-CM-derived exosomes, or a miR in these exosomes, represents a promising scientific strategy to stimulate endogenous cardiomyocyte proliferation. • Compelling preliminary data demonstrate that iPSC-CM-derived exosomes affect CM proliferation, and that these effects are mediated by specific miRs. • The miR molecules used in this study were identified using a stem cell model. In addition, the in vitro evaluation of the effects of exosomes and miRs uses stem cell-derived cardiomyocytes. • The rationale is broadly sound. The only concern is that the lead candidate will be selected entirely based on efficacy data but this ignores the fact that a good candidate must have low toxicity and must be scalable in terms of production of a high quality and consistent GMP product. Narrowing down to a single candidate at this point is therefore risky.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**

Yes: 10	• The project proposes a rigorous and systematic evaluation of exosomes and miRs in stimulating CM proliferation in vitro and in vivo. If successful, the project will lead to a candidate ready for translation (either miR or exosome). • The plans have been well thought through, carefully designed and described in detail. Whilst the workload is extensive, the background data indicate that all the necessary models and techniques are in place to undertake the work. • Experiment design is comprehensive and detailed regarding effects of exosomes and miRs on CM proliferation and function in vitro and in vivo. • Complementary in vitro and animal models are used. • Delivery and release strategies for the exosomes and miRs are underdeveloped. • Consideration of CM hyperproliferation is good and dosing optimization in Aim 3 is one strategy to deal with this. Duration of delivery might be more effective than dosing, though, in providing an activating signal for the desired time window. • How to scale this up in an autologous manner is not well considered. • The choice of autologous iPSC-CM-exosomes is puzzling. This greatly complicates manufacturability and cost, but there is no scientific justification of autologous exosomes compared to allogeneic.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 10	• Milestones are clearly designed around the project goals and appear feasible. • Quantitative success criteria are provided. • The proposal is feasible and relatively low risk.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 10	• Heart disease disproportionately affects underserved communities and a treatment to reverse heart failure would serve this significant unmet medical need. • The project highlights the higher need of under-served communities in relation to heart failure/treatment and the project will specifically utilize cells from diverse donors at the screening stage. • The project proposes to use 2 iPSC lines from Black and 2 from White donors, with 2 male and 2 female. This seems reasonable at this early stage, but doesn't broadly account for diversity.
No: 0	*none*

Application #	DISC2-12669
Title (as written by the applicant)	A novel hybrid CRISPR tool for gene network perturbation and hiPSC engineering
Research Objective (as written by the applicant)	A CRISPR-based tool for simultaneous up- and downregulation of many (~5-20) genes, and a computational tool using scRNA-seq data to predict which genes to perturb for efficacious cell-type conversion.
Impact (as written by the applicant)	A critical bottleneck to the creation of specific cell types from stem cells (and related therapies) is our current inability to make cells execute complex multi-gene programs on command.
Major Proposed Activities (as written by the applicant)	• Develop and characterize a hybrid CRISPR array system for simultaneous up- and downregulation. • Readout of multi-gene perturbation with single-cell RNA sequencing. • Development of a machine-learning computational model for predicting target genes for multi-gene regulation. • Direct hiPSCs into a mesodermal progenitor state using simultaneous perturbation of multiple genes. • Direct hiPSCs into a mature cardiomyocyte state using simultaneous perturbation of multiple genes.
Statement of Benefit to California (as written by the applicant)	This research will lead to the creation of a novel CRISPR-based platform technology to enable the creation of diverse engineered cell types for many applications. These tools can be used to advance understanding of specific cell types and to develop therapeutics that can help Californians. In addition, we will create stem cell lines derived from donors of diverse races, ages, and sexes. This will allow for more personalized therapeutics for underserved populations of California.
Funds Requested	$705,733
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 90

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

Mean	88
Median	90
Standard Deviation	4
Highest	95
Lowest	79
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	12
(1-84): Not recommended for funding	3

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 10	• The proposal seeks to develop a state-of-the-art platform technology for precise regulation of hiPSC differentiation. The platform will lead to production of improved cell lines that can be used for in vitro disease models and drug screening. Indirectly, this will lead to better outcomes in relation to unmet clinical need. • The proposed approach can impact and potentially improve the approach for the differentiation of iPSC cells. Improved differentiation might yield better cells for therapeutic applications. The proposed approach can also produce better differentiated cells for disease modeling, drug or toxicity screening. • Cell based therapies require cells which are differentiated to a precise purity and uniformity. The proposed aims to develop an improved method.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 10	• Overall the underlying rationale is sound. The use of Cas types is novel and the approach for targeting multiple genes is well justified. • The applicants have identified that precise control of cell fate depends on the simultaneous up- and down-regulation of multiple genes. If this can be achieved then it should be possible to tightly control differentiation and to develop differentiation protocols for phenotypes that are currently impossible to achieve. • Existing technologies have two deficiencies. First, it is not possible to up and down regulate at the same time - it is only possible to coordinate upregulation of different genes or to coordinate their down-regulation. Secondly, where coordinated regulation is possible, it can only be achieved for one or two genes whereas precise differentiation needs tens of genes to be simultaneously regulated. The applicants now propose to create a hybrid CRISPR technology, combining up-regulation and down-regulation. They will also build a new computational model based on single-cell data to predict which genes to up- and down-regulate to achieve a specific differentiation outcome. The new approach will be tested for the production of mesoderm lineage and cardiomyocytes. • Unpublished data are presented for a murine ESC line showing that neuronal differentiation can be achieved by up-regulating two specific genes but can be greatly enhanced if at the same time the pluripotency genes are down-regulated. The applicants also describe a new method for enhanced simultaneous CRISPR up regulation of 7 genes. This approach will now be extended to create a novel CRISPR hybrid array for simultaneous up and down-regulation. • The applicants have started to develop their proposed machine learning model for predicting gene combinations needed to drive specific differentiation. Using cardiomycoyte formation as the model, they demonstrated that restricting the modeling to up regulation of genes resulted in optimal but poor effectiveness with two simultaneous genes (further genes leading to inaccuracies in outcome). However, when both up- and down-regulation was allowed in the model then far greater accuracy was obtained. • Under the up- and down-regulation model, the improvements increased with each additional gene, with more limited gains above a certain number. • These preliminary data are compelling and demonstrate feasibility of the approach, though questions remain about how the modeling data translate into practical outcome. This will be addressed in the proposed project. • There is limited preliminary data, especially for aim 2 and also 3. This is presented more as a concept.

No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 8	• The potential of editing a larger number of genes is of great significance. The experimental design is well designed. • The computational model is relatively unexplored and is hugely important for ensuring that use could be made of the multi-gene regulation technology. However, the proposal provides good supporting evidence for the approach and pitfalls/mitigations have been analyzed carefully. It may be high risk but of huge value if successful. • The proposed experiments for aim 1 are well planned and are likely to be an improvement of the current methods. • Aim 2 is underdeveloped. While the proposed network based analysis to identify gene groups is initially logical, the applicants do not fully discuss the complexities. It is likely that a large number of networks will be identified using this approach. The identified networks are likely to represent physiological units necessary for cell function in cells at the present state and defined maturity. It is not clear that the identified gene networks are drivers for differentiation into the desired cell type or maturity state. • For aim 3, the evaluation of the cells is limited to expression analyses. For any cell type this is just one phenotype. Other measurements will be critical to evaluate the differentiated cells more completely. For example for cardiomyocytes, Calcium transients, expression and function of cardiac specific channels and other measurements would be necessary. • It is not clear that the applicants fully recognize the results of network based analysis methods. One might think, serial expression analysis and changes during differentiation might provide more promising gene sets and networks.
No: 2	• For true cell fate differentiation, the cells need to be characterized at the epigenetic level, especially after the genetic perturbations have been removed/turned off.
GWG Votes	**Is the proposal feasible?**
Yes: 10	• The project is feasible. The proposed timelines are appropriate. • The proposal is high risk but feasible. • The team is qualified to conduct the proposed experiments. • The budget, infrastructure and resources are appropriate.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 10	• The proposal addresses these points appropriately. • The proposal can meet the needs of the CA population. • The project does not directly address and account for under-served communities but in time, if successful, could be used to provide personalized medicine approaches that are specific for these communities.
No: 0	*none*

Application #	DISC2-12342
Title (as written by the applicant)	Targeting Critical Regulators of Cancer Stem Cells
Research Objective (as written by the applicant)	We will develop a small molecule inhibitor that blocks the growth of human pancreatic cancer and AML 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 diseases such as AML and pancreatic cancer. In addition, it will improve the prognosis and stratification of patients.
Major Proposed Activities (as written by the applicant)	• Assay Validation: 1) Transfer of activity assays to CRO; 2) Development of binding assay at CRO • Hit validation: 1) Confirm top hits from primary screen in activity assays; 3) Profile top hits in binding assay; 4) Test top hits in cell-based functional assays • Hit series prioritization: 1) Synthesize modified hit compounds; 2) Profile compounds in activity assays; 3) Profile compounds in binding assay; 4) Profile potent compounds in ADME assays • Conditional knockout (KO) mouse generation and characterization • Lead series nomination: 1) Test active compounds/inactive controls in cell-based functional assays; 2) Confirm MoA in cell-based assays; 3) Test top compounds in PK assay in mice (IV and oral)
Statement of Benefit to California (as written by the applicant)	Because this research will lead to development of new treatments for leukemia and pancreatic cancer, the State of California and its citizens will directly benefit. Pancreatic cancer affects people of all genders, ethnicities and socio-economic status. And while AML is the most common adult leukemia, it also accounts for more than 50% of all leukemia-associated mortality in children. Thus, if successful, the new therapeutic will improve outcomes for patients throughout the State of California.
Funds Requested	$1,257,814
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 88

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

Mean	88
Median	88
Standard Deviation	2
Highest	90
Lowest	85
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	15
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 9	• Pancreatic cancer is a very aggressive cancer with poor prognosis. Attacking cancer stem cell function in pancreatic cancer with inhibitors would have a major impact if successful. • Cancer stem cell (CSC) targeting strategies are needed. • This is essentially a drug screening grant that will find drugs that inhibit the targets, which are involved in cancer stem cell proliferation in pancreatic cancer and leukemia. • This grant is mostly a pharmacological screen and compound characterization project that would target cancer stem cells. • The screen progression, lead compound studies and validations, and assays both in vitro and in vivo are good and have a good chance to produce a few high quality compounds that might treat pancreatic cancers and myeloid leukemias by inhibiting the proliferation of CSCs. • It is not clear that there is a therapeutic index for the targeting strategy.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 9	• The role of the target in CSCs suggest that it may be a rational target. • Yes. There is good evidence that the targets are implicated as critical regulators of CSC proliferation. • There is a lot of strong preliminary data in this application. This group has already shown that knockout mice have reduced tumor sizes (5 fold) and there has already been a first phase screen completed from 2 large (several hundred thousand) compound libraries completed.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 9	• Yes. The milestones are sequential, and somewhat mutually interdependent, but this is typical of compound screens and development. There is a fairly good likelihood of this project yielding small molecular drugs that can inhibit CSC function. • There is also a nice proposal to use conditional knockouts to dissect the relative importance of the two genes in humans for their involvement in CSC proliferation. Safety assessment impacts of targeting both genes will be obtained by the conditional knockout mouse studies, and should yield data on the safety of drugs that might extensively ablate function globally. • The use of CROs is appropriate. • The animal model is superfluous as the impact is largely on stem cells and one could test the concept by studying HSCs and NSCs in vitro. • Studies against normal stem cells should be carried out in parallel with the anti-cancer studies.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 9	• The proposal is feasible is based on the preliminary data and expertise of the investigator.

	• Yes. This talented group should be able to be ready to move to translational work after the 2 year timeframe. • Yes. The PI and research team have been instrumental in proving the drug targets for CSCs. The biological mechanisms, compound screens and compound characterization, and safety assessment capabilities are all in place.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 9	• Yes. • No concerns. These drugs are likely to work well in a variety of genetic backgrounds, and further, pancreatic cancer and leukemias are at present under-treated in disadvantaged groups.
No: 0	*none*

Application #	DISC2-12475
Title (as written by the applicant)	Small Molecules to inhibit Nemo-like Kinase for Treatment of Diamond Blackfan Anemia
Research Objective (as written by the applicant)	We propose to study small molecules that inhibit Nemo-like Kinase, to improve the production of red blood cells in bone marrow stem cells of children with Diamond Blackfan Anemia (DBA).
Impact (as written by the applicant)	If small molecule NLK inhibitors are identified that are effective in improving the anemia of DBA and nontoxic, then treatment and transfusions would not be necessary.
Major Proposed Activities (as written by the applicant)	• Treat RPS19 and RPL11 knockdown and normal human cord blood hematopoietic stem cells (HSC) with NLK inhibitors in vitro. (Months 0-2) • Treat HSC from transgenic mice with inducible RPS19 and RPL11 knockdown or normal mice with OTS167 in vitro. (Months 2-6) • Treat mice with RPS19 and RPL11 in stem cell transplant models to determine the efficacy of OTS167 in vivo. (Months 4-18) • Determine the toxicity of OTS167 in normal mice. (Months 6-12) • Study the molecular pathways downstream of OTS167 by RNA-seq and Cytometry Time of Flight (CyTOF) in human cord blood HSC (Months 12-24). • Perform experiments to test with other potential small molecules that target NLK. (Months 20-24).
Statement of Benefit to California (as written by the applicant)	Development of small molecules to inhibit NLK in DBA would result in a significant improvement in the quality of life in these patients. Although DBA is a rare disease, this treatment could also benefit patients with a subtype of myelodysplastic syndrome with del(5q). Development of novel NLK inhibitors could result in a new startup companies, licensing, and create new job opportunities for individuals who live in California.
Funds Requested	$848,098
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 85

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

Mean	86
Median	85
Standard Deviation	1
Highest	88
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. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 9	• This may represent a novel treatment for DBA. • The current proposal seeks to identify novel treatments for Diamond Blackfan Anemia (DBA) which is an inherited bone marrow failure syndrome associated with defects in red blood cell development, congenital abnormalities, and predisposition to cancer. • Current treatments for DBA include chronic blood transfusions, life-long steroids and/or a bone marrow transplantation. These treatments are associated with significant risk of complications and bone marrow transplant is also limited by having available donors. Thus there is a significant unmet clinical need for a new treatment for DBA. • Specifically they will build off of foundational work that the group has lead (and recently published) and identify novel compounds that inhibit NLK as a new treatment for DBA. • The group will also mechanistically dissect the role of NLK in the pathology of DBA thus opening the possibility of identifying new therapeutic targets. • The expected candidate would target HSCs and, if successful, significantly improve patient care and outcomes in patients with DBA. • The application highlights significant background work in which the team has identified NLK as a target for DBA treatment including small molecule inhibitors of NLK. Through a series of very logical, published and unpublished preliminary studies they now have gotten to the point of screening drugs approved by the FDA or in clinical trials for other indications and selecting one for DBA. Thus the premise of the proposal is to facilitate clinical translation.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 9	• The current proposal is based upon a robust amount of published and unpublished preliminary data from the group that support the sound scientific rationale for the proposed studies. • The published work is supportive of NLK as a target. • The published and unpublished preliminary studies support the belief that the research group has all of the resources and techniques required to successfully complete the proposed studies. • Applicants present a very logical progression of preliminary studies leading to two preliminary studies supporting the safety and efficacy of the proposed product they are investigating.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 8	• Yes. Experimental procedures and outcome measures including ability to correct defective erythropoiesis, toxicity, pharmacokinetics, dose range assessment nicely laid out. • It is not clear what will be gained by the studies using the animal models if primary patient samples are available.

	• Likewise, the need for safety and PK studies are unnecessary given that the agent is in human clinical trials. • The need for the molecular characterization (RNA-seq and CyTOF) is questionable. • It may be prudent to carry out studies in Aim 1 and if positive move onto IND filing. This would allow the studies in Aim 2 to be skipped. • Consider revising the milestones around toxicity and molecular pathways (e.g., RNA-seq and CyTOF) to make the proposal more focused on translation. Toxicity is already established and molecular pathways seem to be more basic research oriented.
No: 1	• Some studies (CyTOF, RNAseq) proposed seem not needed.
GWG Votes	**Is the proposal feasible?**
Yes: 9	• The current proposal is based upon a robust amount of published and unpublished clinical data that encourage the reviewer that the group will be able to successfully meet the milestones and complete the proposed studies. • It is based on the previous work of the investigators. • Excellent team. The team has performed the majority of the published and unpublished work to support the feasibility of the proposed project. • Leaders in the DBA field and the discoverers of the importance of NLK in DBA. • Nice letters of support and has arranged for all of the cores and resources needed to complete the project.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 9	• Yes. The team discusses the use of both male and female subjects/mice in the proposed experiments.
No: 0	*none*

Application #	DISC2-12263
Title (as written by the applicant)	Building a hiPSC-based biopacemaker
Research Objective (as written by the applicant)	A proof-of-concept biopacemaker constructed by bioprinting hiPSC-derived pacemaking cells and support cells based on the blueprint of the native pacemaking tissue of a large mammalian heart.
Impact (as written by the applicant)	A hiPSC-based biopacemaker bioprinted using a design of the native pacemaking tissue in the heart, with protective electrical and mechanical insulations, can better sustain the pacemaking function.
Major Proposed Activities (as written by the applicant)	• To make a template for bioprinting hiPSC-based biopacemaker based on the native pacemaking tissue of a large mammalian heart • To develop two bioinks composed of hiPSC-derived cardiac cells for bioprinting biopacemakers • To optimize the printing conditions for the bioprinter • To characterize and assess the function of bioprinted biopacemakers • To test the longevity of the biopacemakers subjected to cyclic stretch in a small animal
Statement of Benefit to California (as written by the applicant)	Over 350,000 patients a year in the U.S. require an electronic pacemaker to restore their heart rhythm. The annual healthcare burden amounts to $20 billion. Repeated surgeries to replace battery and electrical parts generate additional costs and suffering for patients. A bioprinted hiPSC-based biopacemaker can overcome limitations associated with electronic pacemakers, improve the quality of life for the pacemaker recipient, and reduce the cumulative health care costs.
Funds Requested	$1,414,113
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	6
Highest	90
Lowest	75
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	9
(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. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 9	• The proposal is for a novel, bio-inspired 3D printing approach for repair of the sino-atrial node pacemaker. Whilst high-risk in terms of disease-modifying outcome, the project is very well designed and has a good chance of providing proof of concept by the end of 2 years. • At present, cardiac pacemakers are implanted electronic medical devices. This grant proposes to produce pacemaker cells from hiPSCs and this could be curative of cardiac rhythm disorders and also immune-compatible. These would also be free of cable leads. • The goal of producing implantable pacemaker cells is more tractable than full organ engineering, thus impact might come from the tractability of this project. • Biopacemakers would be free from electrical field interferences to which conventional pacemakers are subject. • The 3D printing approach as a platform for therapeutic application and also for in vitro studies is a strength. • This is a good example of adding functionality through cell/tissue therapy. • They will probably arrive at a proof of concept, creative idea. • Innovation is a strength. • Does not address an unmet medical need. • There is no real plan to see if this candidate is actually effective in the treatment of arrhythmias per se.
No: 2	• It isn't clear there is much of an unmet need compared to an electronic pacemaker. But there is a least some (e.g., pediatric). And in the long term, biopacemakers could become more universally competitive.
GWG Votes	**Is the rationale sound?**
Yes: 11	• The approach is to make pacemaking cardiomyocytes in correct configuration and with insulating fibroblasts using bioprinting. At present, this notion is largely hypothetical, but cellular organization of pacemaking cells and insulating cells in 3D space seems reasonable. • The idea that fibroblasts form insulation cells in pacemaker regions is consistent with in vivo histology of endogenous pacemaker regions. • There is some concern that an engrafted biopacemaker may be difficult to interface with extrinsic signaling that ordinarily functions to regulate pacemaking in a normal heart. • There is good preliminary data to show that pacemaking cardiomyocytes can be produced from hiPSCs by this group. • The rationale is that pacemaking cardiomyocytes will perform better and retain pacemaking function longer if they are embedded in a three-dimensional environment that closely resembles that of natural mammalian sino-atrial node. The logic for this bio-inspired approach is sound. The project depends on being able effectively to describe the cell positioning and density through the node as well as reproducing the key extracellular matrix components. This will be particularly challenging. • No clear demonstration of disease modifying activity.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 8	• In preliminary experiments, printed decellularized porcine node versus ventricular ECM were repopulated with pacemaker cells and implanted into mouse diaphragm (to reproduce contraction). In nodal tissue the pacemaker phenotype of implanted cells was

	maintained for longer and calcium signaling showed faster more transient automaticity than in LV tissue. The conclusion is that the ECM is critical for maintaining the function of implanted cells. These preliminary data are persuasive. ● Data provided to show ECM differences between sino-atrial node and control ventricular tissue. The node is richer in fibrillar collagens and elastin and lower in basement membrane related proteins. This suggests that the node cells are embedded in a mechanically protected environment and the applicants hypothesis that this protects the pacemaker cells from mechanical strain due to cardiac contraction (mechanical insulation). ● Porcine sino-atrial node is similar in size and function to human tissue. Preliminary data is provided to show distinct regions with the porcine node. The middle region has aligned cardiomyocytes and fibroblasts whereas in the head and tail of this elongated node the cells are more disorganized. In the head region there is a higher density of pacemaker cells. ● The proposal moves stage wise to implantation of a printed node in the diaphragm of NSG mice. The diaphragm model will enable testing of the node pacemaking activity when in a rhythmic beating environment. The lack of a disease model with implantation in the heart (likely a porcine model) will limit the progression of the work but proof of concept is nevertheless achievable. ● At the end of the grant we won't know if it's disease modifying (only orthotopic transplant studies in the diaphragm without assessment of functionality as an SA node).
No: 3	● This project is at a stage in which cellular and tissue engineering can now be tested, but a sequential research plan (that is quite ambitious in a 24 month timeframe) must be successful at each state in order to yield a candidate ready for translation. ● There is considerable risk in this proposal. Though PCMs have been made and porcine pacemaker regions studied histologically, the project will require several linear and mutually dependent steps to be successful, including bioprinting, validation in vitro, validation in vivo. ● The in vivo test will be to implant the engineered pacemaking bioprinted device into the thoracic diaphragm of mice. Though this will test the ability of the cells to survive contractile stress, there is no real in vivo test of pacemaking function afforded by this approach. This seems like a major weakness, and will result in a failure to be able to assess cardiac rhythm functionality of the pacemaking bioprinted cells. ● The potential pitfall that even a properly constructed biopacemaker might not integrate with the heart properly is not addressed.
GWG Votes	**Is the proposal feasible?**
Yes: 11	● The work is technically challenging but feasible. The aim is to produce a prototype bioprinted pacemaker with designed micro-organization based on natural space-geometry for cells and ECM. A blueprint design will be developed to render thick tissue translucent for imaging. Immunostaining for pacemaker cells, fibroblasts, cardiomyocytes, elastin an collagens I, III and IV will be undertaken. ● The project is very well planned and focuses on the development from background data through blueprint design, generation of prototypes and testing in mice in an atopic (diaphragm) model. There will be no testing at a cardiac implantation site, presumably because this would require a porcine model and is a step too far for this project and time-scale. ● This is an excellent team with proven ability to produce pacemaker cells that are electrophysiologically active. ● High risk high reward but preliminary data demonstrate feasibility. ● Yes, though the project overall is at a preliminary stage (only pacemaker cells have been demonstrated) and all bioengineering and testing must be completed in this research plan. ● The milestones are logical in their organization. However, achieving a validated biopacemaker in 24 months will be quite challenging.

	• The lack of a disease model means that a therapeutic will not have been generated for pre-clinical testing by the end of this project but proof of concept should have been achieved.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 11	• The applicants note that arrhythmias are common in African American populations, and this project might benefit this group. • One of the two cell lines will be derived from an African-American donor. • There is not a great plan to produce cells or test them from a variety of ethnicities and gender, though at the early stage of this work this may not yet be a productive thing to do.
No: 0	*none*

Application #	DISC2-12694
Title (as written by the applicant)	Preclinical development of an exhaustion-resistant CAR-T stem cell for cancer immunotherapy
Research Objective (as written by the applicant)	The expected outcome is an exhaustion-resistant CAR-T cell, which persists long-term in a functional progenitor T cell state in the tumor microenvironment and can be used for cancer immunotherapy.
Impact (as written by the applicant)	CAR-T cells are effective in B cell cancer, but less than 50% of patients experience long-term disease control. Exhaustion-resistant CARs may provide long-term benefit that extends to solid tumors.
Major Proposed Activities (as written by the applicant)	• Establish and optimize a CRISPR-engineered CAR-T stem cell therapy that resists T cell exhaustion. • Perform in vitro evaluation of TEx-resistant CAR-T cell tumor recognition and cytolysis, and progenitor cell state characterization, compared to conventional CAR-T cells. • Perform in vivo evaluation of TEx-resistant CAR-T cell function and persistence in xenograft tumor models, compared to conventional CAR-T cells. • Perform epigenomic characterization of T cell exhaustion in TEx-resistant CAR-T cell in in vitro and in vivo tumor models, compared to conventional CAR-T cells.
Statement of Benefit to California (as written by the applicant)	A significant barrier to long-term efficacy of cancer immunotherapy is the development of T cell exhaustion, which limits T function in the tumor microenvironment. The proposed exhaustion-resistant CAR-T stem cell therapy candidate has the potential to benefit a large population of patients in California who suffer from a broad range of cancers that may be targeted by CAR-T cells, including solid tumors (lung, prostate, sarcoma, and skin) and blood cancers (leukemia, multiple myeloma, lymphoma).
Funds Requested	$1,421,223
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	2
Highest	87
Lowest	80
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	6*
(1-84): Not recommended for funding	8

* See Minority Report below

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 10	• Novel and cutting edge technology addressing the important problem of CAR-T cell exhaustion. • The development of better CAR-T strategies would be clinically useful. • It is not clear that T cell exhaustion is responsible for the majority of failures of these strategies. It would be important to demonstrate that exhaustion is a primary cause of relapse in a specific disease and that the product addresses this disease. • Sarcoma is in need of novel therapies. Less so for B cell malignancies and myeloma. • Not focused on one target; unlikely one mechanism for all cancers.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 9	• The investigators are a major strength of the proposal. The previous clinical development of gene edited CAR-T products that have entered clinical testing is a positive. • Exhaustion may not be the key bottleneck in the clinic for some of the target indications. • Chosen models for preclinical efficacy may not be ideal.
No: 1	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 7	*none*
No: 3	• Given that CAR-T cells produce different outcomes in different diseases suggest that the diseases themselves are important determinants. Thus, the use of a single leukemia cell line expressing target antigens is not sufficient. • The proposal is overambitious by examining 4 different constructs. It may be more useful to study a single one in more detail. Especially choosing a disease in which CAR-T persistence has been found to be a major determinant of clinical outcomes. • There is a lack of focus. Recommend focusing on a single indication. • The epigenetic studies are are somewhat superfluous. • Limitations and pitfalls of the models should be presented.
GWG Votes	**Is the proposal feasible?**
Yes: 6	• Based on the expertise of the investigators, the proposal is feasible.
No: 4	• Phenomenal team. • Too ambitious and unfocused. • Too many samples are proposed for a budget and staff supported by this award. • Very ambitious and not focused (too many models). • Not many pitfalls or limitations discussed.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes:	• Yes.

10	• No concerns.
No: 0	*none*

MINORITY REPORT

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

The minority GWG members thought that this application for exhaustion resistant CAR-T cells for immunotherapy had an extremely strong team and if the problem of cell persistence in immunotherapies could be solved, it would be an important advance for the field. Reviewers acknowledge that cell exhaustion is not the only factor in cell persistence, and also agree that the proposal has a lack of focus with too many targets. However, overall, the minority reviewers thought that the technology, if successful, would have a significant impact on the field as well as being a good fit for CIRM funding as a strong stem cell-focused project, and ultimately voted in support of funding this application.

Application #	DISC2-12714
Title (as written by the applicant)	Developing Cures for Alpha Thalassemia Using Gene Therapy
Research Objective (as written by the applicant)	We will develop and characterize a gene therapy candidate that may be applied to a-thalassemia patient blood stem cells to correct the genetic defect responsible for disease.
Impact (as written by the applicant)	We will develop and characterize a gene therapy candidate that may be applied to a-thalassemia patient blood stem cells to correct the genetic defect responsible for disease.
Major Proposed Activities (as written by the applicant)	• Compare a-globin addition by site-specific integration into the beta-globin locus and by lentiviral transduction of healthy donor CD34+ hematopoietic stem cells to identify optimal method. • Compare a-globin addition by site-specific gene insertion into the b-globin locus and by lentiviral vector transduction of CD34+ HSCs from severe a-thalassemia patients. • Assess effects of each strategy on engraftment and multi-lineage differentiation of a- thalassemia CD34+ HSCs with added alpha-globin gene in competitive engraftment experiments in mice.
Statement of Benefit to California (as written by the applicant)	The prevalence of a-thalassemia is rapidly growing in the United States due to increasing immigration from Asia where a-thalassemia variants are extremely common. In the last 30 years, there has been a 2,000% increase in Asian immigration to the US, with more than half of this growth in the Western US. Thus, patients carrying a-thalassemia mutations now represent a significant public health problem in California, highlighting the need for a modern, curative treatment for this disease.
Funds Requested	$1,063,386
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 80

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

Mean	81
Median	80
Standard Deviation	2
Highest	85
Lowest	80
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	2
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 9	• If successful, the proposed technology will provide a new treatment for alpha thalassemia. Alpha thalassemia is one of the more common single gene disorders with a 5% global carrier rate and higher rates of disease among populations in Southern China and Southeast Asia. • There is a spectrum of clinical presentations of alpha thalassemia depending on the number of alpha globin genes involved. The severe forms of alpha thalassemia require chronic blood transfusions or a bone marrow transplant for treatment/cure. • There is significant morbidity and mortality associated with bone marrow transplants including graft vs host disease, failed engraftment and, furthermore, transplants are limited by finding available/matched donors. • Thus there is an unmet medical need for new treatments for alpha thalassemia. • This would serve as a novel treatment for alpha thalassemia. • A unique comparison of gene therapeutic options. • The application alludes to the success of the current proposal leading to IND enabling studies. Although this progression is not completely laid out, the expertise of the team supports their ability to carry the research to the next stage if, in fact, the proposed studies are successful.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 9	• The scientific rationale for the proposed studies is sound. Much of the rationale is rooted in application of therapeutic strategies for beta thalassemia, which are further along in clinical translation, to alpha thalassemia. • Gene replacement therapy appears to be clinically useful given its application in beta thalassemia. • Good preliminary data supporting the ability to target the beta globin locus for CRISPR HDR. • Good preliminary data on the construction and testing of the lentivirus constructs. • Two of the three milestones call for the testing of the editing constructs in primary cells. There is little to no information given about the availability of these cells and the baseline characterization of these cells including the in vitro and in vivo assays the investigators plan to assess their therapeutics on.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 7	• The strategies proposed are well suited to the investigators. • The project is well planned to develop a candidate that will enable more preliminary safety studies and IND enabling studies not direct to translation. • Additional safety studies will be required including a more thorough analyses of the genotoxic safety profile of the therapies. • The rationale for inserting the alpha globin gene in the beta globin locus is logical. Although the investigators note the potential deleterious effect of disrupting both beta alleles in the "risk" section of the grant, more thorough dose-response studies in the main proposal would strengthen the proposal.

	• More thorough analysis of the safety profile of the proposed therapeutics including viral integration and unintended CRISPR effects should be addressed. • Safety testing (mutational analysis) following engineering should be carried out. • Information about patient derived cells is missing. • Work with patient samples could be better described with more compelling preliminary data. • Other potential pitfalls and alternative approaches are given. • It is not clear what the criteria will be to eventually choose the product between the two strategies. This should be explicitly stated.
No: 2	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 8	• The achievement of milestone 1 is a high probability. • Excellent team. • PI leads a clinical trial for transplantation for alpha thalassemia. • Funds are appropriate for the lentiviral work and the gene editing work. • More info is needed to determine the scope of work performed at one institution and if funds are required to obtain the primary patient cells or if this resource already exists. • The ability to determine if the project will be able to achieve the milestones 2 and 3 within the proposed timeline is limited by the lack of information given and preliminary studies performed on primary patient derived cells. • It would be important to demonstrate that the patient cells are available and can be transduced and/or edited followed by reconstitution of hematopoiesis.
No: 1	• Strong team but limited preliminary data; high risk.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 9	• Yes. • The experimental details do not discuss this.
No: 0	*none*

Application #	DISC2-12499
Title (as written by the applicant)	Developing a common therapeutic for Parkinson's disease and Friedreich's Ataxia
Research Objective (as written by the applicant)	We will use iPSC-derived neurons as a preclinical model to validate small molecules to treat Parkinson's disease (PD) and Friedreich's Ataxia (FA)
Impact (as written by the applicant)	There are many challenges for finding a cure for both PD and FA, due to the lack of effective therapeutic targets. The success of proposal will help develop an effective therapy for both diseases
Major Proposed Activities (as written by the applicant)	• To characterize disease relevant phenotypes • To determine dose concentrations for Miro1 Reducers to rescue phenotypes • To determine the underlying mechanisms for the lead compound • To obtain early safety data • To obtain bio-distribution data
Statement of Benefit to California (as written by the applicant)	About 500,000 Parkinson's disease (PD) patients are currently living in the U.S, and approximate 1/10 of them live in California. Friedreich's Ataxia (FA) is the most common hereditary ataxia that shows pathological features similar to PD. An effective treatment for both diseases is desperately needed. We will identify a therapeutic candidate with the hope to treat both diseases. This study is closely relevant to public health of the state of California and will greatly benefit its citizens.
Funds Requested	$1,421,280
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 80

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

Mean	81
Median	80
Standard Deviation	1
Highest	85
Lowest	80
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. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 11	• This proposal addresses an important area that still (unfortunately) needs new therapeutic modalities, neurodegeneration diseases such as PD and FA. • Small molecule drugs to treat PD or FA would have significant impact on unmet medical need. These diseases have few if any effective treatments. • The application very clearly considers discovery to translation using in vitro tests in human iPSC-derived neurons. Goals are well-aligned with the translational goals of the program announcement. • Creative and translational. • Unifying mechanisms are exciting to explore. • Parkinson's disease application is a strength. • The core of this proposal is finding common therapeutics for PD and FA, two disorders characterized by mitochondrial deficits. Given previous literature on this, there is reason to believe that such therapy would help, at least with some aspects of either disorder. What is less clear are the reasons why the applicants are proposing these two specific models given the wide range of neurodegenerative disease with mitochondrial deficits. • Seem to have a small molecule but not a lot of detail is provided.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 9	• The rationale is sound as both PD and FA have been suspected of having mitochondrial problems • Targeting Miro1 degradation to improve mitophagy is an innovative approach to improve neural cell survival in PD and FA patients. • The project is supported by strong preliminary data showing that Miro1 accumulates on damaged mitochondria, reduces clearance of damaged mitochondria, and is associated with neural cell death upon stress in iPSC models. • The small molecules have modest, but statistically significant, improvement of locomotion in fly models of PD and FA. • The PI has found small molecules that reduce Miro1 levels. These small molecules promote clearance of damaged mitochondria. • PD and FA are complicated diseases with the mechanisms of cell death not completely understood. While mitochondrial dysfunction plays a role, this target may not be limiting for disease progression. Nevertheless, screening and evaluating compounds that improve mitochondrial function is a promising approach. • The rationale for using both is rather weak and focusing exclusively on PD would have, in my opinion, generated a stronger proposal. This is particularly true since the fly model of FA depicts rather subtle behavioural phenotypes and no evaluation of mitochondrial function has been performed to support the proposed mechanism of action. This is especially problematic if, as the applicants state, disease-modifying effects are sought with treatment. • Not clear why PD and FA are studied. • While preliminary data suggests that Miro1 localization on the outer mitochondrial membrane is elevated in sporadic and familial forms of PD, the decision to use only one iPSC line from multiple different familial forms of PD is not sufficiently justified.
No: 2	*none*
GWG Votes	**Is the proposal well planned and designed?**

Yes: 7	• All milestones are well articulated and are moving the needle towards a clinical application. • Subtle phenotype of FA only in flies, not sure why two models are proposed. • There was considerable discussion as to whether the proposal would be stronger if it only focused on Parkinson's disease rather than combining two diseases together. The common mechanism is insightful and interesting but also diverts from focus. Perhaps mention FA as a future direction, or use FA samples as controls, etc. But maybe not both together. • No pitfalls described, not sufficiently powered.
No: 3	• In vitro evaluation of Miro1 reduction small molecules in the iPSC model and fly models is designed to prepare for evaluation in mammalian in vivo models. The project appears well-designed to meet this objective. • The design for treating PD is stronger than for FA. Preliminary data are much stronger for PD and the iPSC lines proposed for PD are more appropriate. • Consideration of neuronal protection under stress is strong. • The project strives for an oral delivery compound but it isn't clear whether these compounds can cross the BBB. • More focus on a single disease and endpoints are needed. • The use/benefits of different genetic iPSC models of PD and FA are not clearly described. • iPSC and fly experiments are not well integrated in their objectives. • More PD cell lines are needed.
GWG Votes	**Is the proposal feasible?**
Yes: 10	• The milestones are well-aligned with in vitro assessment of the Miro1 reducers and movement toward in vivo assessment of the candidate. • The PI has expertise in the model systems used here. The lab has the skills needed to perform the proposed study. • Although milestones have been well described, this is an overly ambitious project especially given that the iPSC FA model has not been established yet. The development and characterization of this model may take significantly more time than the applicants anticipate. The ideas proposed are rather preliminary and the proposal, as a whole, lacks justifications (models, choice of disease, number of cell lines). • All proposed milestones and expected project outcomes are reasonable/logical and based on preliminary data. However, the likelihood of completing these objectives within the stated period is very low given the time-consuming nature of several of the described experiments. Specifically, the completion of model development and validation within a 6-month period seems unlikely. As the remaining protocol is entirely dependent on this step, extending the time to complete the characterization will delay all subsequent experiments. • One potential drawback is the ambitious nature with multiple cell lines differentiated and applied towards the assays. • The investigators do not discuss the fact that they have not yet established the iPSC-based model of FA, and that there may be serious technical challenges associated with this. • For the PD project: Technical pitfalls are limited because the team showed they are capable of producing the proposed outcome measures with at least one iPSC line. • It should be noted that a major pitfall not discussed in the proposal is the inclusion of a single iPSC line for each PD-related mutation. It is the bare minimum to include at least 2 independent lines for each mutation. • Another pitfall is the proposed calculation of sex-based differences. This cannot be done because the proposed experimental design with only one iPSC line/PD mutation is not appropriate for the calculation of sex-based differences. • It is stated in the section Potential Problems & Alternatives that other PD patient lines should reproduce similar behaviors as what has been observed in the cell line. However, different PD-related mutations may differently affect how neurons respond to Miro1 treatments. This needs to be addressed.

	• In the FA part of the proposal, sex-based differences cannot be calculated because of the inclusion of only 3 patient lines (sex is not specified in Table 1). • Success criteria are vague and qualitative. Quantitative success criteria are needed. • More ADME profiling details are needed. • Reasonable for PD but over ambitious for FA.
No: 1	• Overly ambitious.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 11	• Treatments for neurodegenerative diseases would impact all communities. • The applicant has utilized the allocated space for the justification of diversity, equity and inclusion in research to describe, in great detail, how the applicant would implement this in their own setting but also to provide examples as to how they have already done this. A long-term plan is described to ensure that such policies are consistently applied to the research, all this in concert with the institution's program. • If any of the small molecules proposed here were to advance to the clinical setting, diverse population of California would benefit from it, in particular given the fact that small molecules are likely to be more affordable compared to other therapies (e.g. gene therapy, cell transplantation). • The project will address different responses of iPSC lines from male and female donors. However, the male and female lines have different genetic disease mutations so it isn't clear how the investigators will identify effects of sex. • Potential sex differences have been discussed in the grant proposal in terms of statistical analyses, but the proposed experimental plan does not enable the applicant to perform these analyses.
No: 0	*none*

Application #	DISC2-12532
Title (as written by the applicant)	Modulation of oral epithelium stem cells by RSpo1 for the prevention of oral mucositis
Research Objective (as written by the applicant)	Locally delivered formulation of RSpo1 protein as an activator of Lgr5+ epithelial stem cells in chemotherapy- or radiation therapy-induced oral mucositis
Impact (as written by the applicant)	Oral mucositis
Major Proposed Activities (as written by the applicant)	• RSpo1 formulation design and selection for optimal oral delivery • Activation of Wnt pathway by formulated RSpo1 in-vitro • Production of RSpo1 protein • Oral stem cell expansion by RSpo1 to protect and restore chemotherapy and radiation induced oral mucosa damage
Statement of Benefit to California (as written by the applicant)	The proposed research will provide a new therapy for the prevention and treatment of oral mucositis - a common complication of chemotherapy and radiation therapy for cancer patients. If successful, the product development program will also enable growth of the company which will bring more jobs and opportunities for California citizens, as the company is based here.
Funds Requested	$942,050
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	14
(85-100): Exceptional merit and warrants funding, if funds are available	4
(1-84): Not recommended for funding	10

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 11	• Oral mucositis is a severe problem for cancer patients under radiotherapy. Mouth wash can be an alternative to systemic administration of RSpo1 to induce re-epithelization. • Not a novel approach and previously published reports are not cited • Strong potential to benefit patients but potential toxicity not discussed..
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 9	• Hypothesis that stimulation to induce proliferation of epidermal stem cells to induce regeneration of oral epithelium is supported by preliminary data. • Data in murine models is strong. • Strong supporting data.
No: 2	• Recent studies are not cited.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 5	• Organoids from oral biopsies could have been a better model.
No: 6	• The proposal is lacking data that demonstrate that the compound can stimulate human stem cells. This can be accomplish using human biopsies. There is concern that stimulation of stem cells that can result in malignancies. • The risks of the drug are not well considered. • The mouse epithelium is not a good model for a human epithelium.
GWG Votes	**Is the proposal feasible?**
Yes: 10	• It is critical to demonstrate that data in murine models can be reproduced in human. • Please do a more exhaustive search of literature for relevant citations and make sure to cite important papers in proposal so reviewers can be sure you are aware of relevant research. • Make sure to provide a robust pitfalls and alternative approaches section.
No: 1	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 11	• The investigators are proposing that collected samples will include underrepresented minorities. • No concerns.
No: 0	*none*

Application #	DISC2-12612
Title (as written by the applicant)	New noncoding RNA chemical entity for heart failure with preserved ejection fraction
Research Objective (as written by the applicant)	Modified synthetic noncoding RNA molecule
Impact (as written by the applicant)	Heart failure with preserved ejection fraction
Major Proposed Activities (as written by the applicant)	• Lead optimization • Perform extensive preclinical testing and select a therapeutic candidate • Demonstration of injury-modifying bioactivity in a clinically-relevant human progenitor cell population • Optimize formulation and dosing for intravenous delivery, assessing biodistribution • Optimize formulation and dosing for oral delivery • Regulatory planning
Statement of Benefit to California (as written by the applicant)	The target indication is heart failure with preserved ejection fraction (HFpEF), a highly lethal disease refractory to medical intervention. HFpEF is increasing in prevalence, and now accounts for most hospital admissions for heart failure in California. HFpEF disproportionately afflicts disadvantaged populations (women, Blacks and Latinos, and the elderly). Because the therapeutic candidate is universally applicable, the societal benefits of success here are expected to be profound.
Funds Requested	$1,397,412
GWG Recommendation	(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	3
Highest	85
Lowest	75
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	2
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 11	• The application focuses on heart failure with preserved ejection fraction (HFpEF). This is a common condition. The prevalence is likely to increase. There are only a very limited number of treatment approaches available. There is definitely a significant need to develop new treatments. • A molecular therapeutic for heart failure with preserved ejection fraction has the potential for significant impact on an unmet medical need. There are few effective treatment options for this type of heart failure. • The project will develop a noncoding RNA therapeutic that was discovered from a stem cell-derived exosome that demonstrated efficacy in hypertension and hypertrophic cardiac myopathy animal models. • Based on the preliminary data, the candidate factor RNA may have a therapeutic effect on heart failure (HF). • If successful, the proposal could lead to a novel therapeutic entity for the treatment of HFpEF. • It appears that a number or surrogate parameters co-morbid with HF such as impacts on exercise and blood pressure are to some degree corrected by the candidate, and there are also a number of physiological and cardiac tissue ultrastructural changes that suggest efficacy. • The application focuses on drug development processes and also considers distribution. It is clear that the PI is interested in optimizing the candidate as a lead compound for pharmaceutical improvements and delivery. • Translation aspect is a strength: lead compound identified; will evaluate it in two complementary models. • Thoughtful consideration of translation. • The project does not develop a stem cell technology or a stem cell-based therapy. Nevertheless, the biologic developed has the potential to significantly improve patient care by building upon discoveries in stem cells. • Not a stem cell project but enabled by stem cells.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 11	• The proposal will further develop a specific non-coding RNA for the treatment of HFpEF. Strong preliminary data supports the RNA approach. • The rationale seems sound, and based on a fortuitous discovery from previous cells that secrete the candidate, likely in the form of exosomes. • The preliminary data shows that the candidate substantially increases IL-10 production, which likely results in anti-inflammatory activity. • Preliminary data clearly establish that the candidate increases IL-10 secretion by macrophages and elicits other transcriptional changes in target cells. • The premise that cell-derived exosomes mediate heart repair via paracrine effects is strong. • The team is currently exploring exosomes as a treatment modality. Identification of exosome components that mediate biologic activity then engineering these for stability is a sound translational approach. • The candidate is effective in improving function in rodent models.

	• High risk, high reward approach. • There is limited preliminary data on the direct underlying mechanisms. This is of some concern as it relates to the proposed aims and milestones. • The mechanism could be more clear. • There is limited preliminary data on the model. The preliminary data in mice is strong, but the applicants do not provide data on EF/FS/LV function. This will be important to fully establish the phenotype of HFpEF as diastolic dysfunction can also be observed in reduced ejection fraction/HFrEF. • The bulk of this project has moved past using stem cells. The key experiments are in animal models and lead compound optimization. Experiments using cells co-cultured with macrophages have value but are underdeveloped and less crucial than other aspects of the study. • One formulation strategy explored uses exosomes to encapsulate the therapeutic. This is a potentially promising approach but it isn't clear that from a manufacturing viewpoint that the proposed cell type would be the best exosome source. • Lack of mechanism is a weakness.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 9	• The proposed experiments are well developed and supported by strong preliminary data. • The plan to move development from a lead compound to a candidate ready for translation is very clear and well-designed. • The grant is actually quite translational in terms of its research plan, which is mostly focused on lead compound optimization. • The project is constructed to optimize the chemical structure of the RNA-based drug, followed by reasonable assays such as anti-inflammatory effects, and also encapsulation plans, as well as exosome-based delivery approaches. • The proposed experiments on further modifying the target compound appears appropriate. • Modification of the 3' end of the target compound is a good strategy to improve compound stability. • Assessing effect of candidate engineering on macrophage production of IL-10 is logical given this is the hypothesized mechanism of action. Still, assessing more global effects on macrophage transcriptome is probably warranted as well. • The use of complementary mouse/rat models for HFpEF is a strength. This models capture different elements of disease progression. • The in vitro macrophage-cell culture is less well-established. The relevance toward target selection and translation is not clear. Assessments are vague and interpretation of the in vitro results in the context of the in vivo model outcomes are not discussed. • It is not clear that the proposed experiments capture a HFpEF phenotype. The rat model develops cardiac hypertrophy but then also a heart failure phenotype. Timing will be important and additional preliminary data establishing the model would help. • The underlying mechanism and the mode of action for the compound is not well understood. The proposed experiments examine solely expression patterns. The applicants suggest that the candidate affects and directs epigenetic changes. Overall it would feel more appropriate to further characterize the underlying mechanisms before pursuing further optimizing delivery or even regulatory approval. • The study is not mechanistic in identifying how the candidate targets improve HFpEF response. This is a minor weakness since translation doesn't require mechanism identification, but mechanistic studies may be useful in tuning and understanding performance of the therapeutic during translation. • Formulation studies are well-considered. An effective RNA oral therapeutic is a very risky proposition, but there's little harm in trying and comparing to IV delivery.

	• The team poses few alternatives but clearly describes their expected results and how lead compounds and formulations will be chosen.
No: 2	• Not measuring heart failure is a weakness.
GWG Votes	**Is the proposal feasible?**
Yes: 10	• The outcome would be a nucleic acid-based drug, originally enabled by stem cell research, but mostly beyond the scope of cellular therapies now. • Milestones are reasonable and well-designed to move the lead compound to translational studies. • The proposed milestones are well described. They are logical and the outcome is logical. • The team has excellent expertise in translational science. • Yes-this team discovered the candidate and seems qualified. • The team is highly qualified. • The resources are excellent and the budget appropriate. • Some success criteria are quantitative but most are vague and qualitative.
No: 1	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 10	• Treatments to improve heart failure would have a significant improvement of medical treatment of all citizens of California. The team states that heart disease places a disproportionate burden on disadvantaged groups. • The project addresses sex as a biological variable in the rodent models. • The proposal adequately addresses these factors and has the potential to benefit the population of CA.
No: 0	• The diversity plan is very superficial. • Underserved communities have higher rates of untreated heart failure.

Application #	DISC2-12255
Title (as written by the applicant)	Glial-restricted progenitor cells and a gene therapy approach for Rett syndrome
Research Objective (as written by the applicant)	Glial-restricted neural progenitor cells derived from human pluripotent stem cells and a novel AAV vector for Rett syndrome treatment
Impact (as written by the applicant)	Rett syndrome and potentially other neurodevelomental and neurodegenerative disorders.
Major Proposed Activities (as written by the applicant)	• Characterization of the candidate glial-restricted progenitor stem cells and AAV vector. • Transplantation or AAV infection in human Rett syndrome brain organoids. • Transplantation or AAV infection in the brain of a mouse model for Rett syndrome. • Measure the cellular, physiological, behavioral and survival impact of the two treatments. • Prepare and organize the next steps using adult mice and large animals.
Statement of Benefit to California (as written by the applicant)	Brain disorders are responsible for more years lost to disability than any other medical condition. Cell and gene therapies to understand and treat rare single-gene disorders such as Rett Syndrome will provide the tools and methods that will ultimately be used to address the more common complex brain disorders. In fact, MECP2 mutations are not restricted to Rett syndrome but also autism spectrum disorders, affecting 1 in every 54 births worldwide.
Funds Requested	$900,000
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 80

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

Mean	80
Median	80
Standard Deviation	3
Highest	84
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. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 9	• Development of treatment for Rett syndrome (RTT) represents an unmet medical need. This is a syndrome based on mutation in MECP2, and developing ways of overcoming deficiency in this protein is the likely path forward. • Rett syndrome is a rare disease with no cure. • Based on their previous work, the applicant proposes to develop and validate 2 distinct approaches, i.e. gene therapy using AAV to modulate the main mutation within astrocytes or the transplantation of healthy human glial-restricted neural progenitor cells (GRNPCs) to regulate the functionality of glial and neuronal populations within the Rett brain. • Proposal is focused on proof of concept by developing two different therapeutic approaches- cell transplant and astrocyte specific AAV vectors gene therapy. The use of a specific promoter to drive the gene replacement mainly in astrocytes, and leverage the strong non-cell autonomous component of this condition is quite exciting. • Novel idea of targeting the astrocytes. • Males have been excluded from most approaches due to severity and rarity, applicant plans to include males in their clinical approach. • This approach could represent a successful stem cell therapy, but the experiments conducted thus far are not sufficient to be clear whether this is the case.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 9	• This proposal is based on the general idea that astrocyte dysfunction underlies several neurological conditions including Rett syndrome. By targeting astrocytes, either by gene therapy to increase expression of MECP2 or by the transplantation of human astrocyte progenitors, it is hypothesized that neuronal health will be beneficially impacted. • Restoring function in GRP derived astrocytes (AAV vectors) will rescue RETT neuronal phenotype and would solve the issue of having to over-express MECP2 in neurons which is difficult to regulate. • The rationale for this proposal is that wild type astrocytes can rescue properties of neurons with mutations in MECP2. This is biologically interesting. In addition, the ability to rescue function of mutant astrocytes with AAV infection is also interesting. The question is whether these observations are therapeutically interesting. One of the main problems is the question of when transplants will be carried out. Thus far, experiments have been carried out too early to be able to tell whether they will be useful in the actual disease case. • RTT is diagnosed at an average age of 2.7 years, which is approximately equivalent to a one month old mouse or rat. Thus far, all experiments have been conducted at much earlier stages. In addition, experiments on organoids also represent attempts to introduce corrections during embryonic development. The real question is not whether you can prevent the neuronal defects that occur in mutant neurons, but whether you can reverse them when they already have occurred. In this context, there are no rescue experiments. • Some solid preliminary data. However, a weakness is there is no relevant preliminary in vivo data. It is not clear why the applicant did not do at least a mouse to mouse transplant of wild type astrocytes into the MECP2 mouse brain. • While abnormal glial responses are increasingly being recognized to play a role in neurodegenerative diseases, the therapeutic approaches proposed here will need significant improvements and considerable development to advance to clinical trials. For

	example, a major drawback is the use of male models to test the therapeutic strategies for a disease that primarily affects females. • AAV-mediated expression of MECP2 is driven by the promoter, but it is unclear whether the promoter is adequately active in neonatal mouse astrocytes to express disease-modifying levels of MECP2. • The proposed development of an AAV-based treatment for patients will necessitate considerable additional work to address (i) the specificity of the promoter and the severity of off-target effects, (ii) the possibility of varying levels of promoter activity in different regions of the brain and the resulting change in MECP2 levels, (iii) the safety profile. At this stage, the proposed work is a proof-of-concept study with important limitations and conceptual flaws. It also needs additional preliminary validation.
No: 1	*none*
GWG Votes	**Is the proposal well planned and designed?**

Yes:
5
	• In addition to the rationale concerns, there is no quantitative information on cell migration, proliferation, etc.
	• Overall the approach is clearly laid out but there are still some weaknesses:
	  • The expectation is that human astrocytes replace the mouse endogenous astrocytes, as shown in Figure 8. However there they use a wild type mouse, the number of astrocytes is not quantified and only a small region is shown which raises questions about dissemination.
	  • Advantage of one approach versus the other not clear.
	  • Applicant expects reversal of some symptoms but time line, severity or what symptoms specifically is not addressed.
	  • Applicant addresses single cell sequencing in the pitfalls but no such experiments are proposed
	  • Opportunity to assess changes at therapeutically relevant doses is discussed but dosing itself is not addressed.
	  • Potential over-expression of MECP2 in AAV targeted astrocytes and associated defects are not addressed, Figure 6 only show successful re-expression.
	  • Transplantation in MEPC2 brain organoids shows astrocyte differentiation but the onset of the disease is postnatal and organoids might thus not capture the right time point of the disease.

No:
5
	• The preliminary data demonstrates that the team possesses the technical expertise to carry out this project (iPSC-based technology, organoid and mouse models, cell transplantation, AAV treatment) and that the project is accordingly feasible.
	• The data provided demonstrate that restoring expression of MECP2 in astrocytes successfully rescues neuronal function and survival in the iPSC-based Rett model.
	• However, the preliminary data failed to demonstrate that the AAV infects a large proportion of astrocytes in the neonatal brain. There may be concerns regarding levels of GFAP promoter activation in the post-natal context, specifically. It would also be important to know what proportion of astrocytes (and in which brain region) need to be transduced to successfully rescue neuronal death.
	• The migration of astrocytes in the brain should be considered.
	• In general, the experiments are superficially described and important justification omitted.
	• Experiments only in male animals is a weakness.
	• Additional technical issues include:
	  • Pooling mice litters. Despite the fact that grouping animals from mixed litters will be performed early post-natally, males tend to fight more and this may create a problem. There is also a chance that the mother may not accept the new pups.
	  • The organoids should include microglia to account for possible neuroinflammation.
	  • There are no details/explanation as to how the applicants will evaluate the presence of undifferentiated cells after transplantation.

	• It is unclear why the investigator proposes to stop the AAV in control at 4 weeks of age and not at 33, 35 and 36 weeks (end of experimental treatments). • It is unclear when they will use KO vs. mutant MECP2 in the in vitro experiments, the proposed model changes between sections. In Aim 1, it reads "We will transplant control cells into MECP2-KO brain organoids" (page 18), but they later write "GRNPCs will be transplanted into diseased (MECP2 mutant) brain organoids" (page 23). Are these MECP2 mutant lines derived from patients or are they in fact the MECP2-KO lines? • The applicants propose bulk RNA-seq of mouse brains, but single cell RNA-seq would make more sense to enable a cell type-specific assessment of transcriptomic changes as a response to treatment. • Page 18: the applicants mention the use of primary isogenic fibroblasts but isogenic lines are usually prepared at the iPSC stage. There were no indications that they have made or will make these isogenic fibroblasts.
GWG Votes	**Is the proposal feasible?**
Yes: 8	• Overall, the work envisioned in this proposal is ambitious but feasible within the timeline mentioned here, given the preliminary data and expertise. • Experienced investigators. • Reasonable goals. • Weakness in milestones: In case the transplantation does not show the expected result the applicant proposes to increase cells or alter the timing - there is no compelling reason for this as it could turn out that astrocytes do not disseminate in the MECP2 affected brain or the restoration of function needs to be region specific. • Although a number of pitfalls are raised, such as the exclusive use of male models when the disease primarily manifests in females and the selection of GFAP as a promoter, the rationale for continuing with these problematic designs is not sufficient for the seriousness of the concerns raised. These are major issues that have unfortunately flawed the basic design of this proposal. • The pitfalls of transplanting into an appropriately aged animal, of reversing damage that has already occurred by this stage, the effects of the disease processes on the behavior the transplanted cells (particularly when damage has already occurred) are not addressed. Thus, in respect to development of a clinically useful product, thus far there is no test of the key hypothesis.
No: 2	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 9	• These rare syndromes do not select for race, ethnicity, etc. That said, all research of this nature will deliver products that are immensely expensive, which will always be a problem for underserved communities. • While Rett is more common in females, the in vivo data presented in the application are only using males for ease of approach. Future approaches, however, will include female mice. It is arguable that the initial focus on males is a strength as most existing approaches have a bias toward females and often exclude males due to the severity of the pathology.
No: 1	• The exclusion of female models is particularly concerning given that the target patient population is female. If the investigator moves forward with this male-oriented model, experiments will need to be repeated in a female model. This approach would ultimately delay clinical translation. • The influence of race, ethnicity, sex and gender has superficially been presented by the applicant with a succinct account of how he would address ethnicity and gender diversity within his own research group. The applicant has provided examples as to how the applicant has, and will continue to be conscious of these inclusion criteria with the recruitment of students from various countries. However, the project plan does not discuss how the proposed research will address diversity-related issues.

Application #	DISC2-12370
Title (as written by the applicant)	An hematopoietic stem-cell-based approach to treat HIV employing CAR T cells and anti-HIV broadly neutralizing antibodies
Research Objective (as written by the applicant)	We propose to transduce hematopoietic stem cells with vectors that encode chimeric antigen receptors targeting HIV for T cells and anti-HIV broadly neutralizing antibodies for B and/or plasma cells.
Impact (as written by the applicant)	Recent methods are limited by the rise of escape mutants against a single CAR. Our approach solves this issue by the ability to express multiple CARs and multiple secreted bnAbs concurrently.
Major Proposed Activities (as written by the applicant)	• HSC vector construction and evaluation. • Evaluate CAR T and B cell activity. • Determine whether populations of dual HSCs are effective at controlling HIV-associated viremia and reducing the proviral reservoir.
Statement of Benefit to California (as written by the applicant)	HIV is a devastating viral disease that affects over 135,000 Californians and well over a million Americans. Though antiretroviral therapies have significantly reduced the severity and transmissibility of the disease, a cure still remains elusive and anti-HIV drugs need to be administered for life. These drugs have been associated with significant toxicity. If the studies proposed here are effective in animal models and then translate to humans, a cure is envisioned.
Funds Requested	$1,143,600
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 80

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

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

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 10	• Strategies for achieving a drug-free HIV remission or functional cure are of the highest priority to the field. The proposed strategy has the potential to achieve this. Although stem cell therapy may not be a cost effective option in the short term, if successful additional efficiencies and optimization of the treatment would likely follow ultimately making such a therapy competitive with the costs of long-term ART. • The ability to provide a cure for HIV would be notable.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 8	• Yes. The major innovations here are transduction/transfection of HSCs and adding constitutive expression of broadly neutralizing antibodies to CAR-T cells. On the negative side, CAR-T cells have not yet shown much activity in vivo in HIV infection. • The use of CAR-T and broadly neutralizing antibodies is feasible. • The greatest issue is that it is not clear whether the engineering that will be carried out will disrupt HSC function. Preliminary data is needed that HSCs that express both CAR-T and secrete mAbs still function as HSCs (i.e., differentiation potential, long-term hematopoiesis, and self-renewal through serial transplantation). Without this data, the grant is too speculative. • There is a concern that the construct will be silenced over time.
No: 2	• Panel is not sure if introduction of the transgenes would negatively impact stem cell function.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 8	• Very well written. Very dense, but well thought out in many areas. Excellent controls for in vivo experiments. Excellent consideration of alternative approaches. The suggestion to try non-neutralizing antibodies for the CAR is particularly interesting. • One issue the PI should note, emerging data indicate that the replication competent reservoir does continue to decay over time in people living with HIV on ART and this is related to virus expression. • Another issue the PI should be aware of is that no humanized mouse models recapitulate the secondary lymphoid tissue microenvironment found in humans and large animal models. However, large animal models are too expensive to perform these proposed experiments, and rationale for use of humanized mice is acceptable. • As long as the needed HSC preliminary data are provided.
No: 2	• Preliminary data on proper HSC function after transduction needs to be provided to establish the feasibility of the plan. • Cell lineage-specific promoters should be discussed and considered to preserve HSC function. • Preliminary data need to be presented better.
GWG Votes	**Is the proposal feasible?**
Yes: 7	• Ambitious, but appears feasible with staffing and resources. More concrete information regarding the volume of animals that the core facility can accommodate would strengthen it. • The proposal is feasible.
No: 3	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**

Yes: 10	• The PI missed the opportunity to point out that HIV disproportionately afflicts non-white individuals and gender minorities in California. Specific statistics on the relevance of this intervention long term for these populations would strengthen the proposal. • The PI could likely get information from commercial HSC providers regarding the distribution of race/sex in their donors, which would also strengthen the proposal. • Yes.
No: 0	*none*

Application #	DISC2-12580
Title (as written by the applicant)	Key Tools for Spermatogonial Stem Cell Therapy
Research Objective (as written by the applicant)	The two goal of this project are to: (i) purify human spermatogonial stem cells (SSCs), and (ii) define a protocol to culture and expand human SSCs for future therapeutic applications.
Impact (as written by the applicant)	This proposal directly deals with 2 bottlenecks holding back SSC therapy to treat infertility: (i) no known SSC-specific markers, and (ii) no reproducible and robust protocol for human SSC culture.
Major Proposed Activities (as written by the applicant)	• Screening candidate human SSC-specific protein markers encoded by genes exhibiting preferentially expression in primitive undifferentiated spermatogonia, based on published scRNAseq analysis. • Determining the degree of SSC enrichment (using a functional assay) of human testicular subsets purified using SSC markers identified in this study. • Using RNAseq analysis to define a "SSC signature" of human SSCs. • Using the SSC signature to develop a PCR assay to specifically detect human SSCs for future clinical applications. • Leveraging a short-term human SSC culture system developed by the applicant, along with transcriptome data implicating specific signaling pathways, to develop a robust in vitro SSC expansion system. • Determining the molecular fidelity of in vitro cultured human SSCs.
Statement of Benefit to California (as written by the applicant)	Approximately 7% of men of reproductive age in California (>1 million men) are not able to father children after 1 yr of trying (defined as "infertility"). SSC therapy has the potential to provide fertility for many of these infertility cases. One application of SSC therapy is to provide fertility to men rendered infertile by chemotherapy to treat cancer or other conditions. Towards this end, testes biopsies are already being banked from individuals receiving chemotherapy in California.
Funds Requested	$780,180
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 80

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

Mean	80
Median	80
Standard Deviation	0
Highest	81
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. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 9	• At present, pre-pubescent males harbor only immature SCCs, and these individuals are rendered effectively infertile by chemotherapy treatments. This roadblock would be removed if this grant is successful, insofar as isolating, validating, culture and expansion of SCCs is concerned. There is no such bottleneck for adult males needing chemotherapy, as sperm is routinely frozen prior to chemotherapy that might induce infertility. • Ultimately, the goal is to produce mature sperm from testes samples from pre-pubescent males, who have compromised infertility due to chemotherapy. This is a rather specialized group, but an unmet need. (In the case of mature males, sperm can simply be obtained and frozen prior to chemotherapy, which is a routine and established treatment). • The project may yield progress leading to the ability to treat male infertility by isolating spermatogonial stem cells (SSCs) from testes biopsies, then produce mature sperm from these. • The grant, surprisingly, does not include a plan to see if SSCs are functional (having the ability to undergo differentiation leading to the production of mature functional sperm (either in vitro or in vivo), thus the progress of the grant will be somewhat incremental, even if the stated goals are achieved. • The ultimate goal of achieving spermatogenesis from the isolated SSCs is not addressed in this grant, and thus, a full plan and vision for translation will still not be in hand upon completion of the proposed work. • "Device/Diagnostic/Tool Candidates" vs "Therapeutic Candidates": sometimes the applicant writes towards one of these, sometimes towards the other. Seems to me this is a therapeutic candidate. • I am not sure a product can be developed on CIRM's "urgent" timeline.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 9	• Yes-the rationale is straightforward. At present, markers of SCCs are poorly defined. This grant proposes to use scRNAseq to improve the situation regarding definitive markers of SCCs, then develop ways to induce these to undergo differentiations and spermatogenesis in vitro, yielding mature sperm for use in IVF. • The preliminary data shows competency with isolation of candidate human SCCs and xenograft experiments resulting in humanizing of immunodeficient mouse testes. In addition, several candidate SCC markers have been identified. • There is also some progress in culturing putative SCCs over longer periods of time, indicating that the research team can optimize culture conditions for development of directed differentiation protocols, and to improve yield and survival of SCCs. • No great markers for (SSCs) exist. This is both an opportunity for the proposal but also a problem. Clearly the field needs better markers. It is a worthy goal to find them. But what if these markers cannot be found? Or it takes a really long time to find them? Then the downstream aims cannot be done. • The rationale is that they can find a set of mRNA expression markers that sufficiently distinguish SSCs to enable their enrichment. It is possible that rational is sound, but it isn't clear to me that the authors acknowledge that it might not be possible to do what they wish solely based on RNAseq. • Aim1 Potential Pitfalls and Alternatives section claims that there will not be any, other than possible difficulty in finding commercial antibodies once markers have been

	identified. But what if they are not identified? What if expression profiling cannot adequately enrich for SSCs? • Figure 1 claims 6 clusters. I see two fairly distinct clusters and a third ring that cannot obviously be divided into separate clusters. So maybe 3 clusters. • Figure 3 does not show a 38 fold enrichment of cells. Of the 12 data points, 6 are above the clusters from the controls. That is a twofold enrichment.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 6	• The aims are logical. Milestone 1 is to find markers to define undifferentiated spermatogonial cells, and in milestone 2 and beyond, engraftment and gene expression/pathway assays based on xenograft-mediated repopulation will be used to correlate the expression of candidate markers with engraftment. • The is a very straight forward adult stem cell grant. Overall the approach is reasonable, whereby a functional assay will be used to identify markers, followed by attempts to isolate and culture immature SSCs. • The xenograft assay endpoint is based on morphology and location. Though not sophisticated, the location and appearance of mature SCCs is well known and this should serve as a reasonable endpoint for the assays. • The marker has already been shown to provide a 38-fold enrichment in SSC formation in the xenograft assay. It is possible that this is already a sufficiently good marker, which makes some of the work in Aim 1 perhaps superfluous.
No: 3	• Functional studies could be improved. • Statistical analysis is not well described. • "To avoid potential sampling biases, each replicate will contain cells from at least 3 independent fertile individuals." by using RNAseq instead of scRNAseq, applicants gain several advantages. However, they also will be dealing with cells in aggregate which means they need to deconvolute the contributions of mixtures of different cell types. This is not insurmountable. However, by mixing cells from different individuals, they compound the difficulty by now having to deconvolute the contributions from different individuals. Their stated purpose in mixing cells from different individuals is to avoid "sampling bias". But If sampling bias is a problem, it needs to be discovered. If it is a problem, it means the methodology as a whole lacks robustness. Better to do three separate RNAseq samples than to mix 3 individuals together. • "Successful RNAseq analysis, as defined by typical metrics, including PCA analysis of variability between replicates" PCA is not a statistical methodology. It is a dimensionality reduction procedure. So it is not appropriate as a "success criterion."
GWG Votes	**Is the proposal feasible?**
Yes: 9	• Yes, this project can proceed fairly quickly, as there are no lengthy cell culture and engraftment studies proposed. • These are feasible goals, as progress has already been made on all 3 of the objectives. • It would be nice to define success. Exactly what level of enrichment in the functional assay would constitute success for each aim and sub-aim of the proposal? • "Generating a human SSC PCR assay by selecting primer pairs specific for genes exhibiting selective expression in human SSCs" Is this done? Seems error prone, because very few transcripts are perfectly selectively expressed in a particular cell type.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**

Yes: 9	• Yes, the surgeon involved in the grant has a clientele with a large proportion of Hispanic and African American individuals. Obviously, this grant is confined to treatment for biological males. • Yes, this is a general approach.
No: 0	*none*

Application #	DISC2-12588
Title (as written by the applicant)	Metabolic targeting of pancreatic cancer stem cells.
Research Objective (as written by the applicant)	We plan to develop therapeutic antibodies that will enable the elimination of pancreatic and liver cancer stem cells by starving them to death.
Impact (as written by the applicant)	Our research products will revolutionize the treatment of primary and metastatic pancreatic and liver cancers.
Major Proposed Activities (as written by the applicant)	• Development of function blocking monoclonal antibodies that will cut off energy supply to pancreatic and liver cancer stem cells. • Development of function blocking nanobodies that will cut off energy supply to pancreatic and liver cancer stem cells. • Confirm the ability of these antibodies/nanobodies to kill cancer stem cells in combination with other drugs. • Determine the therapeutic impact of these antibodies/nanobodies on human pancreatic cancer grown in mice.
Statement of Benefit to California (as written by the applicant)	Pancreatic and liver cancers are highly aggressive and difficult to treat, resulting in high mortality rates. Both of these cancers disproportionately affect economically disadvantaged ethnic minorities in California, including African Americans and Latinos. Our research and development efforts will lay the foundation to new pancreatic and liver cancer therapies that in addition to saving lives will reduce treatment costs.
Funds Requested	$1,425,600
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	4
Highest	84
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. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 10	• Pancreatic cancer is a lethal cancer the makes use of a robust cancer stem cell (CSC) pool. This grant may result in ways to starve pancreatic cancer CSCs by blocking two modes for their nutrition. • This is a CSC treatment approach, and the grant may result for treatments to eliminate or inhibit the survival of pancreatic cancer stem cells. This could significantly improve patient care outcomes for a very problematic cancer. • The need to eliminate cancer stem cells seems clear for many cancers, but these cells are resistant to existing therapies. Thus, this represents an unmet medical need.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 8	• Yes, this PI and co-workers have previously demonstrated, in a published article that CSCs normally rely on one pathway for energetics, but inhibition of this pathway induces a parallel pathway for nutrition allowing their survival. This grant proposes to pharmacologically inhibit both pathways to see if this dual treatment can starve pancreatic CSCs. • The application is based on interesting findings on the importance of two pathways in cancer stem cell and cancer cell function. • Since only a single rather non-specific inhibitor of the nutrition is available, part of the proposed work is to develop antibodies and nanobodies as biologics for the inhibition of relevant molecules. • The problem is that this grant is proposed as targeting cancer stem cells, but the data that would support such a target are almost entirely lacking. • Thus, there is a need to carry out some of the well accepted experiments that are used to test the hypothesis that CSCs are being targeted. • There is also a lack of attention to the fact that the pathways being targeted are of great importance to normal cells. • In addition, syndecan is a shed protein. Is this going to be a problem? It is not discussed.
No: 2	• The specificity of the mechanism to cancer stem cells is not clear given the preliminary data.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 3	• The preliminary data is both extensive and strong. In the preliminary data (much of it already published in good journals), the applicants show that CSCs utilize two sources of energy based pathways. • The preliminary data also shows that combined treatment with inhibitors severely inhibits tumor growth, though this requires the use of some drugs that lack specificity. • Aside from the uncertainty of getting the reagents they need, the plan is straightforward. • There are experiments needed to determine if they really are targeting CSCs.
No: 6	• No clear indication whether they target cancer stem cells
GWG Votes	**Is the proposal feasible?**
Yes: 9	• Developing antibodies and nanobodies that target membrane proteins is a good approach, and forms the basis for therapeutics development in this grant. • Assays of efficacy of antibody and combined chemotherapeutic treatments are strong, and include the use of organoids, slice cultures, and tumor assays in NSG mice with human xenograft tumors.

	• The applicant should be able to address the concerns about whether they are targeting CSCs and truly decreasing tumor recurrence. • One of the cores of the CSC hypothesis is that you can shrink a tumor by 98% but if you don't get the cells with CSC properties, the tumor will recur. Thus, a demonstration of eliminating CSCs is very important, particularly if this is going to fit with the CIRM mandate to focus on stem cell related issues. • The grant seems to be devoid of clearly identified pitfalls and alternatives, which is surprising given the otherwise excellent quality of the grant, preliminary data, and research plan.
No: 1	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 9	• Pancreatic cancer is actually quite prevalent in underserved communities, so this is an important cancer across the board for improving treatment.
No: 1	• Pancreatic cancer therapies are underutilized in disadvantaged groups, so this grant could increase the treatment of pancreatic cancer, which is especially prevalent in African American populations. • The CSC lines to be tested are limited in number, and therefore not representative of broad groups based on race or biological sex.

Application #	DISC2-12603
Title (as written by the applicant)	Therapeutic targeting of Glioblastoma Stem Cell survival and self-renewal signaling
Research Objective (as written by the applicant)	This DISC2 tests a strategy to target survival and self-renewal in glioma stem cells (GSC), and will identify a therapeutic candidate for safety, dosing and efficacy testing.
Impact (as written by the applicant)	The glioma stem cell (GSC) population is resistant to radiation and DNA-targeted chemotherapy agents, driving tumor recurrence, and few therapeutic strategies have targeted GSC.
Major Proposed Activities (as written by the applicant)	• Investigate C3a-C3aR signaling in additional primary glioblastoma (GBM) cell lines in vitro, testing effects on proliferation, survival, self-renewal and metabolism. • Complete in silico design and screening of 100 RNAi candidates targeting C3aR expression with preliminary validation of sequences in HeLa cells, and 20 RNAi candidates for dose/cellular toxicity. • Complete testing of two different conjugate chemistries for GBM cell transfection and therapeutic candidate distribution after in vivo delivery. • Complete in vivo proof-of-concept testing for preliminary efficacy of 3 RNAi therapeutic candidates in combination with FLASH irradiation in an orthotopic GBM transplant model.
Statement of Benefit to California (as written by the applicant)	Glioblastoma (GBM) is the most common, aggressive, and lethal primary brain tumor. GBM has a median survival of 18-24 months. 70% of GBM patients exhibit progression/recurrence by 1 year after diagnosis and tumor resection, with less than 15% of patients surviving at 5 years. The glioma stem cell (GSC) population is associated with resistance to conventional therapy, contributing to tumor recurrence and emphasizing the need to target GSC to achieve effective treatment.
Funds Requested	$1,348,874
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 80

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

Mean	80
Median	80
Standard Deviation	0
Highest	80
Lowest	80
Count	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. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 11	• Glioblastoma is a major problem with no cure or significant disease delaying therapies. The best outcome to date is extension of lifespan by approximately 2.5 months. • The biology of C3-C3aR is fascinating and warrants further investigation on the basic science and translational science levels. • Developing better treatments for GBM is an important goal. • The PI plans to target GBM stem-like cell function with modified RNAis that will block activation of the C3-C3aR pathway. This pathway is demonstrated to be required for full GBM stem-like cell activity.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 9	• Exciting approach with a very intriguing biology. • Targeting GBM stem-like cell behavior is critically important. • Targeting the C3-C3aR pathway to target stem-like cell function is well supported. • The consideration of intraventricular administration with or without intratumoral administration would potentially address GBM dissemination. • There is no data that would suggest that C3a blockade can affect established tumors in vivo, not clear whether anti-sense treatment would be sufficient to reach all cells in the tumor mass. • There is no data presented that would suggest that injection of iRNA would specifically target GSC.
No: 2	• At the moment, not enough information is provided to know if this is sound. • The single treatment experiment in vivo is based on treatment at the same time as cell transplantation. This has no relevance to the realities in the clinic, where the tumor is established and disseminated in the CNS. • They have not shown elimination of tumor initiating cells, which requires treatment before transplantation and then maintaining animals long enough to look at delayed tumor growth. • Need to test treatment for longer time points and with high receptor expression. • I also note they did their experiments in vivo on the CD133-low population. There is also the concern that CD133 is one of many GSC markers, and it's clear this group is heterogeneous and also does not capture all the tumor initiating cells.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 8	• With the exception of the clinically relevant concerns, the biology of the proposal is very nice. • The proposal is well-designed but is weakened by the absence of some key preliminary data. The only in vivo evidence for activity is in a xenograft model in which the GBM isolate is treated prior to implantation. This is not adequate. A demonstration that an established tumor can be treated with the approach is required for support of the approach. • A more comprehensive evaluation of C3, C3a, C3R in patient tissue specimens, especially with regard to stromal cell expression should be done.

	• The applicant does not make a good use of cell lines expressing high versus low levels of CD133 cells. For example, if elimination of the GSC is the main focus why is the candidate screening performed in a cell line with very low CD133 expression? • Self-delivering siRNAs, which do not require transfection reagents or delivery vehicle, are effective in in vivo applications, including the CNS. • The application uses an RNAi approach to target human GSC that have been generated as cell lines. The product does not involve stem cells.
No: 3	• Preclinical and preliminary data is not compelling enough. • Milestone 3 should be done earlier.
GWG Votes	**Is the proposal feasible?**
Yes: 9	• The proposal is technically feasible. • Milestone 3 is interesting where the applicant will transplant GBMs and then deliver the lead compound to the same coordinates 7d post-tumor cell implantation. This is the main experiment that would define whether the approach is valid - not sure why this is milestone 3 rather than milestone 1?
No: 2	• The generation of the RNAis are feasible. Injection is feasible. Whether this will exhibit anti-tumor effect in an established tumor is unknown and in some measure should be established prior to embarking on the project. • The need for continuous treatment to prevent re-emergence of stem-like cell function from the more differentiated GBM cells will need to be addressed. • Treatment of disseminated GBM at the time of recurrence will need to be addressed. • Lack of efficacy data in mice.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 11	• GBM does not select for any particular populations. • Treatment would be available to everyone. • A more comprehensive evaluation of patient specimens might yield some insight into whether this pathway is differentially expressed/activated in different genetic ancestries or in males versus females. • Yes, to the extent that a study with limited numbers of cell isolates can.
No: 0	*none*

Application #	DISC2-12358
Title (as written by the applicant)	iPSCs as a screening tool to predict risk of nonalcoholic fatty liver disease
Research Objective (as written by the applicant)	The objective of this proposal is to established undifferentiated iPSCs as a diagnostic tool for the prediction of nonalcoholic fatty liver disease onset and severity.
Impact (as written by the applicant)	Despite the widespread estimated prevalence of NAFLD, there are currently no tools available to predict likelihood of NAFLD susceptibility beyond standard clinical and demographic information.
Major Proposed Activities (as written by the applicant)	• Create an iPSC-based NAFLD risk score (iPSC-RS) by defining threshold values for oleate-induced intracellular lipid accumulation that distinguish iPSCs from NAFLD patients versus healthy controls. • Validate the iPSC-RS in an independent set of iPSCs from 25 NAFLD cases and 25 healthy controls, and evaluate the it's reproducibility across biological replicates and independent laboratories. • Compare the validated iPSC-RS to other NAFLD risk predictors based on genomic information alone.
Statement of Benefit to California (as written by the applicant)	Nonalcoholic fatty liver disease (NAFLD) is a widely undiagnosed condition, and is estimated to impact up to 30% of adults. NAFLD is most prevalent in Hispanics, with the absolute highest levels found in individuals of Mexican ancestry, and thus is relevant to California's LatinX population. As NAFLD is anticipated to become the leading cause of liver transplant, identifying Californians most at risk could address significant gaps in screening and prevention for this serious disease.
Funds Requested	$813,000
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 80

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

Mean	79
Median	80
Standard Deviation	7
Highest	90
Lowest	70
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	5*
(1-84): Not recommended for funding	9

* See Minority Report below

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 9	• NAFLD is major unmet clinical need. Developing new prognostic/diagnostic approach would be useful. • There are no standard-of-care pharmaceutical treatments for NAFLD. A promising pharmaceutical needs more clinical studies before there is enough evidence to know its value. Clinical trials are often prohibitively expensive unless a good diagnostic tool can be employed to recruit/screen trial participants. Thus, this diagnostic tool could break a key bottleneck limiting drug development. • There are NAFLD "mimic" diseases that are life threatening and treatable. An improved diagnostic for NAFLD should help with the differential diagnosis of these rare life-threatening liver diseases. • In the absence of pharmaceuticals, therapy for NAFLD focuses on managing co-morbid conditions and lifestyle modifications (e.g., diet). A good diagnosis is very important to guide and motivate these lifestyle modifications. • In the long run, many other conditions may be diagnosable by assays on iPSCs (and differentiated cells), enabling multiplexed diagnostics, reducing costs and greatly expanding the utility of this type of test. This proposal pioneers this frontier and is very innovative. Such assays are currently an unmet promise of stem cell science, and this application directly addresses CIRM's mission. • This proposal aims to create a diagnostic test for NAFLD. • It might take a long while before this test gets validated, approved, and deployed in clinical practice, but in the meantime, the test could accelerate clinical studies. • Using undifferentiated cells is a weakness.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 3	• The applicants have confirmed expression of NAFLD disease factors in undifferentiated iPSCs in their preliminary data. Furthermore, they also show in preliminary data the ability of their assay to differentiate in iPSCs the differential effects of mutant (NAFLD causing) and non-mutant variants of these genes. • If for some reason, in some other setting, these genes are not expressed in iPSCs, the authors have the ability, as they demonstrate in a recently published paper that they can differentiate cells into hepatocyte-like cells, in which these genes are also expressed - giving them another option for this promising assay. • By looking at enzymatic functions in real cells, this assay avoids the error-prone efforts of bioinformatics to try to understand the disease consequences of mutations from sequence data alone. Thus, a functional representation of the genome is achieved without having to wait for an individual to grow to adulthood. This assay should largely reflect the direct genetic contribution to risk, which is a primary driver of NAFLD.
No: 6	• Unfortunately, using undifferentiated cells has little biological relevance and the information generated will be difficult to apply in the clinical context. • Differentiated cells should be used rather than undifferentiated iPSCs. • Fatty accumulation is only one aspect of the disease. Inflammation and fibrosis play a key role in NAFLD progression. These aspects will not be modeled by lipid accumulation in iPSCs. • Having a prognostic score system for NAFLD based on iPSC is likely to be difficult to integrate in a clinical pipeline. When do you screen your population?

GWG Votes	Is the proposal well planned and designed?
Yes: 8	• "If we fail to identify a clear threshold, we will extend our NAFLD cases to the remaining 17 iPSC lines [...] along with matched controls." Decide how many you are going to do up front and stick with it. For these statistical analyses, it is not valid to keep increasing sample size to multiple analysis halting points until significance is achieved. • "To assess whether the cutoff scores differ by sex and/or genetic ancestry, when sufficiently powered, we will perform analyses split by sex (or genetic ancestry where sufficiently powered) to assess whether different thresholds are identified." Are you sure you have enough power for this? Aren't you more likely to find random fluctuations falsely attributed to these factors if you subdivide your sample? • "It is possible that the iSPC-RS [sic] does not perform equally in between ancestry groups. In this event, we will estimate genetic ancestry using the genome-wide genotype information, and include ancestry principal components in the model." Given that most polygenic risk scores (PRSs) have ancestry biases, it would seem that if you see a bias in a combined score it is due to the PRS. It isn't clear how using principal component analysis would correct for a PRS bias (which already has implicit ancestry in it due to the weighting on the PRS coefficients). Maybe the correct thing to do if you see such biases is to drop the PRS component of your combined risk score. Also, if you do add ancestry principal component analysis to your risk score, the cost of the score goes up (at least for now) as you would have to get the genotypes on everyone tested. • Please consider appropriate abbreviations. Abbreviating "risk score" as RS may not be necessary.
No: 1	• The proposal only relies on hPSCs which have limited relevance to hepatocytes, the main cell type targeted by NAFLD.
GWG Votes	**Is the proposal feasible?**
Yes: 8	• The proposal is feasible. • The project is straightforward.
No: 1	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 9	• The focus on different ethnicity is important and well included in the study. • Yes. Very much so. Polygenic risk scores are notoriously biased against non-Europeans as they are almost always to-date derived from European populations. By developing an assay rooted directly in the target phenotype, the proposal avoids the genetic-ancestry biases of PRSs.
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.

Minority reviewers acknowledge that the applicants are testing complex liver metabolism in undifferentiated iPSC. However, they thought the preliminary data presented were compelling. In particular, minority reviewers disagreed with the majority concern that iPSC do not express the relevant liver pathway genes. Minority reviewers thought that the genes involved in NAFLD are expressed in the iPSC, and that the differences in lipid accumulation shown in iPSC variants supported this. Minority reviewers thought that prior experiments showing a lack of expression of a particular gene in a particular cell type doesn't mean that gene is not expressed at all in that cell type, and even very low levels of expression of a gene can have profound molecular phenotypes. In addition, the applicant had submitted a post submission published paper that directly addresses the concern of lack of expression of the liver genes, as it offers the use of iPSC derived hepatocyte-like cells. Thus, minority reviewers were convinced by the strong preliminary data of the proposal, and ultimately voted in favor of funding.

Application #	DISC2-12271
Title (as written by the applicant)	Neural stem cell exosome therapy for COVID-19
Research Objective (as written by the applicant)	We propose here to engineer neural stem cells to produce anti-SARS-COV-2 exosomes. We will harvest these immunologically inert exosomes to treat COVID-19 disease.
Impact (as written by the applicant)	The largest bottleneck we forsee is generating of a GMP grade factory to make these anti-COVID exosomes. This can be overcome by development of GMP space, much like current immunotherapy spaces.
Major Proposed Activities (as written by the applicant)	• Characterize the anti-inflammatory, cell modifying properties and effects on cellular networks resulting in those cells treated with anti-CoV-2 NSC exosomes. • Characterize the NSC secretome, genomic payloads and transcriptomic programs affected by nanobody exosome exposure to immune cells. • Develop NSC-exosomes capable of inhibiting CoV-2 replication by delivering anti-CoV-2 siRNAs and asRNA 800bp packaged RNAs to virus infected cells. • Screen the top bimodal (siRNA or antisense RNA) NSC- derived exosomes for repression and neutralization of CoV-2. • Characterize the top-candidate CoV-2 targeted bimodal exosomes in K18-hACE2 mice • Characterize the top-candidate CoV-2 targeted bimodal exosomes in CoV-2 infected Hamsters.
Statement of Benefit to California (as written by the applicant)	This project will benefit California by providing a therapeutic to treat COVID-19 disease. There is currently no cure for COVID-19 and this proposal will develop a targeted therapeutic that can be readily generated and administered to COVID-19 patients. This product can also be used outside of California, easily shipped and administered to others suffering from COVID-19 disease.
Funds Requested	$1,141,776
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	5
Highest	87
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. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 12	• There is still a big need for therapies to treat patients with COVID19. In the present proposal, genetic manipulation of neural stem cells will allow the applicants to generate receptor-target exosomes that will deliver specific micro RNAs to control viral replication • Antivirals and therapeutics are still needed for COVID-19 disease despite recent vaccine successes. • COVID-19 is a problem. • This project might produce exosomes prepared from NSCs that have some therapeutic and antiviral effects on COVID-19 disease. • If anti-SARS-CoV-2 exosomes are produced, the translation is obvious as a therapeutic. • Potentially very novel. • The only connection to stem cell research is the use of NSCs for exosome preparation. It is not clear why NSCs would be preferable to many other cell types that could be used for exosome preparation.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 11	• There is some preliminary data to show that exosomes can be made that have Spike protein embedded in their membranes, which should target exosomes to ACE2 (spike receptor) expressing cells. There is also some mouse data to show the ADME characteristics of NSC-derived exosomes in mice, especially upon concentrations within whole body distributions. This group has also made progress in producing exosomes that contain siRNAs targeting conserved regions of SARS-CoV-2 RNA. • Parts of the rationale are sound, and parts not as much: Producing spike protein targeted exosomes seems like a good idea, as is the packaging of anti-viral RNA targeting siRNAs. However, there is a lot of research proposed on evaluating anti-inflammatory and secretome-content and modulating effects of the exosomes and treated cells, and these do not seem as directly relevant to therapeutic efficacy designed to directly inhibit SARS-CoV-2 RNA. • Overall sound rationale, but critical preliminary data are missing. • It is not intuitively obvious why NSCs are a good choice to produce exosomes with cargo that might target SARS-CoV-2 RNA. Justification for the use of NSCs is not well developed, and rests mostly on the notion that NSCs (and exosomes derived from them) are not terribly immunogenic. • The use of neural stem cells is not justified, also there is no preliminary data that demonstrate that the proposed modifications work. • Not clear why using NSC for respiratory diseases; strength is cGMP cell source.
No: 2	• There is a lack of preliminary data supporting the rationale. • The rationale for the use of starting cell population is unclear.
GWG Votes	**Is the proposal well planned and designed?**
Yes 9	• For the most part, yes—the outcome might be effective for exosomes produced from NSCs, though the use of NSCs for packaging seems to be the only connection to stem cell research in this grant. • There are no concerns. The proposed experiments are elegant modifications of the source cells that will result on cell-target exosomes with an enriched cargo to control viral infections.

No: 4	• Aim 1 seems out of scope: omics studies not useful for treatment development. • Aim 2 does not include testing in human pulmonary cells.
GWG Votes	**Is the proposal feasible?**
Yes: 12	• Yes, the exosome expertise in this is very strong, and the work flow seems reasonable. • Yes, the group is well qualified to conduct the proposed experiments.
No: 1	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	• This aspect is not particularly relevant for this study at this early stage, but eventually efficacy for diverse groups would be needed after an IND, that will be enabled by this grant. • COVID-19 is more prevalent in underserved minorities
No: 0	*none*

Application #	DISC2-12398
Title (as written by the applicant)	A Fluorescence Lifetime Imaging and Cell Microarray System for Metabolic Tracking and Manipulation of Hematopoietic Stem Cells
Research Objective (as written by the applicant)	We will develop an imaging-based tool to enable rapid and non-invasive tracking of stem cell function in blood stem cells, to enable their quality control and expansion for bone marrow transplantation
Impact (as written by the applicant)	It will enable rapid assessment and screening of optimal culture conditions for blood stem cell biomanufacturing and quality control for bone marrow transplantation and gene therapies
Major Proposed Activities (as written by the applicant)	• Define metabolic stemness in human hematopoietic stem and progenitor cells • Enrich human hematopoietic stem cells (HSCs) by their metabolic stemness • Evaluate the function of metabolically enriched HSCs in vivo • Determine single-cell metabolic/phenotypic transformation of cultured HSCs • Determine metabolic profiles of parent and daughter HSCs in culture • Evaluate the changes of division patterns upon metabolic drug treatment.
Statement of Benefit to California (as written by the applicant)	In bone marrow transplantation, finding HLA-matched donor HSCs is crucial for the success of the procedure. Californian population has become more diverse and multiracial, making donor-matching even more difficult. Expanding HSCs ex vivo will create an off-the-shelf cell bank with unlimited supply, but has not been achieved due to lack of tools to rapidly track HSC stemness in culture. We will overcome this barrier by developing a non-invasive, real-time imaging tool to measure stemness in HSCs.
Funds Requested	$823,312
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	84
Lowest	75
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 9	• This is a very innovative application bringing a new insight about the biology of stem cells and coupling it to cutting edge technology to potentially revolutionize the field. Such technological innovations can completely change research, either by opening up new directions of inquiry or by dropping the cost of existing approaches and enabling not just incremental but paradigm-upsetting changes to a field. • Identification of metabolic potency metrics has the potential to accelerate development of HSC-based therapies by improving the quality of cells that patients receive. • The overall goal of the project is to identify metabolic optical biomarkers that could improve the ability to identify stemness in a heterogenous mixture of HSCs. • Development of a screening platform for metabolic drugs that induce/maintain stemness has the potential to improve use of HSCs and to facilitate their expansion ex vivo. • Efficient screening of HSCs would address a major bottleneck in HSC generation and preparation. • The metabolic optical biomarker analysis is rapid, label-free, and nondestructive. • Integrated analysis/separations platforms could be used downstream of cell expansion. • This is a very early stage discovery project. The translational plan is vague. It isn't clear what will/could be translated based on the results of the project. • A more focused approach on technology development that could be integrated into stem cell therapies would better fit the mission of this program. • What is the projected throughput? Will the anticipated throughput be high enough for the technique to be useful?
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 9	• The use of Fluorescence Lifetime Imaging and Cell Microarray (FLIM) to identify metabolites is a powerful approach to monitor aspects of metabolic activity at a single cell basis. FLIM allows rapid, nondestructive monitoring of autofluorescent metabolites. • The team has developed a microarray platform to capture and analyze immobilized single cells, and to track FLIM measurements in mother and daughter cells during and following division. • There is a strong linkage between metabolic activity and stemness that warrants further exploration. • The use of simple machine learning models is a logical way to identify metabolic discriminators of stemness. • The investigators provide strong preliminary data, largely in mouse HSCs, supporting the proof-of-concept of using FLIM to discriminate between HSCs and differentiated cells. • Proof-of-concept data is provided that suggests certain drugs affect metabolic phenotypes, although the lack of identification of these drugs makes it difficult to determine if these are expected results. • There was concern among the panel that fluorescence lifetime imaging had been attempted for many years by many groups, all ending in failure. Thus, this application may need more justification of "why this approach will succeed, given that many others have failed". • Linear discriminant analysis (LDA) is not that much easier to interpret than a support vector machine (SVM). And if a SVM gives a much better resolution, you would be sacrificing a ton of clinical value for this minor improvement in interpretability. Indeed why is interpretability critical here? If you could sacrifice interpretability for improved clinical outcome, wouldn't you take it?

	• Why not try some other algorithms? Neural net? Random forest? The number of variables is unclear, and a critical flaw in the research aims.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 4	*none*
No: 5	• The project is very well-designed to test hypotheses about the linkages between FLIM measurements and stemness in HSCs. • Clear hypotheses are presented and supported by the preliminary data. A logical and innovative plan is provided to test the hypotheses. • The use of machine learning models to distinguish populations is a strength. There are minor concerns about using markers as ground truth given the desire to outperform surface markers. Retraining the model based on phenotypes might be appropriate. • The project design does not convincingly establish a candidate ready to advance to translation. The goals are to demonstrate proof-of-concept in human HSCs but relatively little technology development is proposed. • It isn't clear whether the technology for further development would be metabolic imaging technology, separations technology, a drug screening platform, or something else. A more focused plan is needed. • The array-based capture and separation method is highly innovative but lacks a development plan needed to advance the technology. This includes design specs and a way to optimize these to compete with other cell separation technologies. • Objective 2 (Milestone 4 and 5) studies are well-designed but lack a relationship to translation. It isn't clear how information about heritability of metabolic programs will be used. • The drug screening approach is underdeveloped. Will the drugs be chosen to complement the hypotheses tested in this proposal? Is this a HTS platform proof-of-concept? • The throughput and cytotoxicity of the platform need to be better considered and discussed. • The technology is a major strength of this application. However, the cursory effort (and lacking expert guidance) of the computational biology in the last aim was a major anchor. This was my major problem with the proposal. • The material on discriminant analysis does not seem to have deep understanding. I recommend pulling in someone who can give really good advice on this topic before settling on a particular approach. • Fewer acronyms please.
GWG Votes	**Is the proposal feasible?**
Yes: 8	• The milestone plan is clearly defined and seems achievable. • Success criteria do not benchmark against gold-standard technologies for identifying stemness and separating cells (e.g. FACS). • The project seems feasible.
No: 1	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 9	• HSCs will be obtained from a de-identified population, but one that reflects the diversity of California. • Improved HSC quality would benefit the diverse population of California. • This technique is generally applicable.
No: 0	*none*

Application #	DISC2-12354
Title (as written by the applicant)	Quantitative & High Throughput Hematopoietic Stem Cell Purification
Research Objective (as written by the applicant)	This proposal is for a manufacturing tool to more rapidly and efficiently purify stem cells from blood.
Impact (as written by the applicant)	Implementation of this tool can reduce production cost and enable more customized & precise stem cell therapies to be made.
Major Proposed Activities (as written by the applicant)	• Demonstrate the capability of the ratcheting system to isolate rare stem cells • Demonstrate scalability to large blood quantities • Show superior performance compared to competing technologies • Demonstrate capability to sort multiple cell types at once • Demonstrate large scale sorting of multiple cell types at once
Statement of Benefit to California (as written by the applicant)	Development of this technology will work synergistically with other cell therapy production efforts to reduce the cost of cell therapies and make them more accessible to underserved socio economic groups in California. Furthermore, the company is a small business located in San Diego, CA and can greatly benefit the state with this proposed technology by providing jobs and expanding the capabilities of cell therapy production facilities in the state.
Funds Requested	$499,414
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	8
Highest	88
Lowest	60
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. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 10	• This technological platform is aimed to advance the current state of clinical cell sorting and disrupt one company monopoly in magnetic cell sorting. • The proposed technology is addressing a number of critical bottlenecks in clinical cell sorting, namely: (1) low purity of magnetically sorted cells, (2) low cell yield (recovery), inability to sort for more than one surface marker at the time, and (4), long duration of the cell sorting process (slow speed). • Yes. Faster, larger scale, more efficient, less expensive methods are needed to purify stem cells for therapeutic and research applications. • The proposal is significant for the cell therapy field as a whole rather than specific to improvements in HSPC transplantation. • Yes. Purification is a critical bottleneck. • New sorting device with high throughput potential to optimize cell therapies. • Bringing variety to the field is important. • The impact on HSPC transplantation field is overstated. There is a standard technology available on the market which works well. Also, graft engineering is taking a specific tight niche in HSPC transplants, since unmanipulated hematopoietic grafts frequently work well and there is no need for cell selection. • The proposed technology would be more impactful in the immune cell therapy field, such as CAR-T, other T-cells, NK cells, TILs, DCs... • The clinical significance of purging tumor cells in hematopoietic graft is unclear. • Impact is overstated, niche project.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 9	• The scientific rationale is sound. The technology behind the platform, developed by PI, is not described in great detail in the application, but referenced and linked to the publications. • There is a lack of preliminary data. Figures 4 and 5 are just explaining the technology. Figures 6 and 7 present data on T-cells. No single preliminary experiment on HSPC is presented in order to support further development and highlight potential advantages of the method over current technologies (such as purity). • Supportive preliminary data but relevant comparison is missing. • I would like to see a bit more text on the choice of antibodies and how the labeling will be performed. Most of the text assumes this has already been done, and starts by describing the machine and physics. • There is a lack of information about reagents which will be used in the proposed research plan. For example, sourcing of antibodies and magnetic beads of different sizes. The manufacturer and grade of these reagents are unknown, but this is a very important part of the development of commercial platform technology as a whole. • If the authors are trying to compete with the existing standard platform, they need to make sure that not only performance of the instrument has the advantage, but develop similar or better reagents (antibody, beads, buffers...). Think about it as a novel platform, not just a device. • The authors mentioned that the cost of the procedure would be lower compared to existing clinical magnetic cell sorting platform, but they did not discuss how they are planning to achieve it. The lower cost is one of the most important reasons for the development of new competing technology. • Multiplexing would be a possible potential advantage but the number of markers that can be used is not clear.

	• Multiplexing is the main advantage of proposed technology over existent technology. However, multiplexing capabilities are not well described (with exception of figure 7). Can the platform handle 3 or 4 or even more markers? Perform positive and negative selection at the same time? • The very low purity of T-cells in figure 6 looks very different from the competitor T-cell isolation kit - Is it a lack of reproducibility of the competitor's protocol? Please clarify. • "Because magnetic activated cell sorting selects from all magnetically labeled cells, it cannot distinguish between off target cells and rare target ones which drastically reduces purity (~10 to 50%) for rare cell types (Fig. 3)." It can distinguish but there is reduced purity. This has to do with differential input amounts, not ability to distinguish.
No: 1	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 4	• Some experiments are not well designed. For example, instead of mixing leukopacks with tumor cell lines, the authors should get leukopacks from patients with hematologic malignancies. Such products are available from some vendors. It will be a better representation of real clinical material, since tumor cells change morphology and function compared to normal blood cells, which could impact cell sorting parameters. • Another important experiment should be a head-to-head comparison of large-scale clinical sorting of CD34+ cells by proposed device versus existing clinical scale technology. Instead of this important experiment, the authors propose to have small scale run to compare their prototype with research-grade kits from two companies. The latter company is not even on the market for clinical cell sorting. • The function of sorted cells should be assessed with in vitro (colony forming units) or in vivo assays. • The project timeline could be shortened to 18-20 months. • I'd recommend to skip tumor purging part and focus on (i) chip design and optimization of high speed sorting of leukopacks with 5-10 billion total cells, (ii) head-to-head comparison with competitor instruments and (iii) sourcing reagents.
No: 6	• The biology of the purified HSCs needs more characterization. • The study plan should include multiplexing with more antibodies. • More technical information needs to be provided to allow evaluation. • No details of reagents used. • No safety study of beads. • "Proposed tool is upstream of patient in workflow therefore minimal safety issues." There can be safety issues even upstream of the patient. What if the therapeutic is toxic? One of the first comments in the proposal is, "Although magnetic tagging could be considered as a disadvantage because of the beads, this method is FDA approved and has been extensively used in isolation of different cell populations, including HSPC" wouldn't this be considered a safety issue, even if FDA approved? • Many of the figures can be improved. Legends don't adequately describe the figures and points being made. Axes and labels of graphic elements are not always clear or appropriate. Perhaps have someone with experience in writing grants could give the proposal a brief read for style and presentation. • KPI acronym not defined the first time it was used. Please avoid all unnecessary or unusual acronyms.
GWG Votes	**Is the proposal feasible?**
Yes: 8	• The proposal is feasible. • The project seems straightforward.
No: 2	*none*

GWG Votes	Does the project serve the needs of underserved communities?
Yes: 10	• This is a universal technological platform • This tool is generally applicable.
No: 0	*none*

Application #	DISC2-12639
Title (as written by the applicant)	iPSC extracellular vesicles for diabetes therapy
Research Objective (as written by the applicant)	We will derive extracellular vesicles from induced pluripotent stem cells (iPSCs), characterize the content and immunomodulatory activity of EVs, and deliver iPSC-EVs to treat Type-1 diabetes.
Impact (as written by the applicant)	Type 1 diabetes (T1D) is an autoimmune disease and there is no therapy to preserve islet cells. Accomplishment of this project will generate a new therapeutic modality for T1D treatment.
Major Proposed Activities (as written by the applicant)	• EV isolation, characterization and reproducibility • Scaling up EV production in a bioreactor • Analysis of iPSC EV content and identification of the components for EV quality control • Development of a hydrogel delivery platform for EV delivery and prolonged presentation • In vitro assessment of immunomodulatory properties of EVs and development of in vitro functional assay • Evaluation of safety and immunomodulatory properties of iPSC EVs in vivo in T1D mouse model
Statement of Benefit to California (as written by the applicant)	Type 1 diabetes (T1D) is an autoimmune disease characterized by the destruction of insulin-producing beta cells by patient's own immune cells. This project aims to develop cell-free immunomodulatory therapeutics based on the extracellular vesicles (EVs) secreted by induced pluripotent stem cells (iPSCs) to treat T1D. This project will develop a new therapeutic modality for the treatment of T1D and autoimmune diseases, and will benifit our citizens and healthcare in California and beyond.
Funds Requested	$1,345,756
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	6
Highest	90
Lowest	70
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. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 10	• This is an impressive application.The approach is innovative and could provide new weapons to inhibit autoimmunity. The choices of what data are likely to be important make sense. • Modulation of immune response in patients with type I diabetes have some potential to have some benefit. • Immunomodulatory therapies to stop autoimmune destruction of endogenous beta cells and/or prevent recurrence of autoimmunity after autologous SC-islet transplantation could benefit patients with T1D. • Extracellular vesicles (EVs) from iPSCs have higher immunomodulatory potential than EVs from MSCs. • Bioreactors could help with scale-up and translation of iPSC-derived EVs. • Biodegradable hydrogels could provide sustained delivery of iPSC-derived EVs reducing dosing. • Patient specific iPSC-derived EVs will increase the cost of the procedure. • Very limited discussion on clinical translation and how EVs will be matched to patients. • Discussion on scale-up and dimensions of bioreactors to produce clinically relevant amounts of iPSC-derived EVs is missing.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 7	• The preliminary data are strong. The applicant seems comfortable woking with IPSC-EVs and it is impressive that they can increase the proportion of Treg cells. Also, when administered in a hydrogel to mice, the development of diabetes was delayed. • The use of stem cells is fundamental to the approach - the idea is that extracellular vesicles (EVs) from iPSCs will work better than those from MSCs.
No: 4	• EVs secreted by cells under dynamic conditions (bioreactors) have the same hydrodynamic diameter, and iPSCs cultured under dynamic conditions secreted about twice as many EVs as under standard static conditions in 24 hours. • Analysis of iPSC and MSC-EVs show that while both of the EVs contain many of the common EV proteins, their composition is quite distinct. iPSCs can be expanded indefinitely while MSCs cannot and their phenotype is less variable than MSCs. • To address short half-life of EVs after their administration in the body requiring higher dosage and frequent administration, sustained release from biomaterials will allow reducing dosing and off-target effects. • MS analysis of iPSC-derived EV still need to be optimized to identify those factors that determine their immunomodulatory properties. • A functional in vitro assay that can be routinely used to evaluate the functional variability between EV on both mouse and human T cells and macrophages is proposed but preliminary data shown in Fig.1E,F do not contain important details (murine or human) or statistical comparisons. • Incidence of diabetes after single administration of iPSC-EVs encapsulated in hydrogel shown in Fig1-Aim 3 does not show statistically significant or meaningful improvement. • The group has not characterized the exosomes, they have not worked on the bioreactor and they do not have a protocol to isolate the exosomes.
GWG Votes	**Is the proposal well planned and designed?**

Yes: 2	• The application clearly describes the approach, which is logical. • The plan is very well thought out. Each milestone is clear and to the point. • More could have been done with pitfalls, but that is not serious concern. • Autoimmunity of diabetes has proved to be particularly difficult problem and has been a major impediment to beta cell replacement success. The timeline is ambitious but may be OK.

No:
9
	• Preliminary data is very slim, no preliminary data demonstrate a beneficial effect after diabetes has been established. Also there is no in vivo data on the target cells.
	• Characterization and consistency of the iPSCs and EBVs need to be demonstrated.
	• Strengths include:
	  ◦ Detailed description of statistical analysis.
	  ◦ Adequate description of methods for optimization of EV isolation.
	  ◦ Optimization of dynamic iPSC culture previously performed.
	  ◦ Comprehensive integrated analysis of the vesicular transcriptome and proteome and miRNA knockdown studies to determine immunomodulatory mechanisms.
	  ◦ Tunable release of EVs from hyaluronic acid (HA) hydrogels is sustained up to 7 days and dependent on the presence of hyaluronidase.
	  ◦ Whole blood test to evaluate iPSC-EV toxicology profile in mice was previously optimized and safety of iPSC EV+ Hydrogel injected subcutaneously confirmed.
	  ◦ Utilization of two T1D models in mice: adoptive transfer of diabetogenic splenocytes in mice and spontaneously diabetic mice.
	• Weaknesses include:
	  ◦ Details on bioreactor used are missing; not clear if the optimized conditions can be scaled-up.
	  ◦ Targeted EV release for HA hydrogel optimization is not specified; many conditions will be tested in parallel but the desired release kinetic is unknown.
	  ◦ Treg induction assay should include Treg suppression assays to check for Treg functionality.
	  ◦ For biodistribution studies, IVIS detection may not be sensitive enough to detect EV other than in the injection site.
	  ◦ Phenotypical characterization of EV treatment in the T1D models in mice are limited; insulitis should be quantified blindly in treated mice and controls; T cell immunophenotyping should be done also in the pancreas where diabetogenic T cells will be found after activation and expansion in PLNs.
	  ◦ Very short section on potential pitfalls with little feasibility of proposed alternative approaches.
	• In the document, figures go from 3 to 8, missing 4,5,6,7. However, no pages are missing.

GWG Votes	**Is the proposal feasible?**
Yes: 8	• This is a proposal from a group of very accomplished scientists. A lot of work is proposed but it should be possible to carry out this work during a two year period. • PIs are outstanding accomplished scientists and the postdoctoral fellows seem very competent.
No: 3	• Yes for Milestones 1, 2, and 3. Milestones 4, 5, 6, 7 still require optimization of the hydrogel. • PI has over two decades of experience and expertise in engineering stem cells, immune cells and biomaterials for regenerative medicine applications. • Multidisciplinary team includes experts in the area of bioengineering and cell engineering, biomaterials, drug delivery, immunoengineering, immunology and diabetes animal model. • Postdoctoral researcher has extensive research experiences on drug delivery and EVs. • Excellent environment. • Adequate budget

	• Because the lack of characterization of exosomes, and the lack of preliminary data, this is a high risk proposal. There are concerns because of the lack of preliminary data that justify the experiments. As is described in the application, the investigators will work on:
	  • Optimal method for EV isolation, they don't have a defined protocol on the isolation.
	  • The EV composition will be carefully characterized, they don't know how to induce modulation of inflammation.
	  • Immunomodulatory effects of iPSC-EVs will be evaluated. The protection of EVs have not been well characterized.
	  • Biomaterial delivery platform will be designed. They have not defined the way to deliver the cells.

GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 10	• iPSC lines for EVs isolation are highly representative of the diverse Californian (and USA) population, and cover male/female (two for each) and three races (Caucasian, African American, and Hispanic/Latino). • It could be very important for type 1 diabetes but less so for the more common T2D. • Very short section.
No: 1	• Not discussed.

Application #	DISC2-12708
Title (as written by the applicant)	Development of Improved Stem Cells for Cardiac Cell-Based Therapy
Research Objective (as written by the applicant)	Conditioned stem cell-derived cardiomyocyte that is resistant to cell death, leading to enhanced stem cell survival and retention for cardiac transplantation.
Impact (as written by the applicant)	A high rate of transplanted stem-cell loss after transplantation to treat heart failure is addressed in this proposal by developing stem cells that can survive better in the host myocardium.
Major Proposed Activities (as written by the applicant)	• Validate the critical roles of key proteins in stem cell derived cardiomyocytes to enhance their survival post transplantation. • Elucidate RNAs that are differentially expressed in age-matched male and female control stem cell-derived cardiomyocytes compared to activated cells from different ethnicities. • Successful modification of stem cell derived cardiomyocytes to produce candidate therapeutic cells. • Delivery of conditioned stem cell-derived cardiomyocytes in mice followed by bioluminescence imaging to quantify stem cell retention. • Determine cardiac structural and electrical remodeling post transplantation. • Determine the improvement of cardiac function post transplantation.
Statement of Benefit to California (as written by the applicant)	Cardiovascular disease causes more deaths in California than all cancers combined. Since cardiac myocytes have limited ability to regenerate, a significant loss from myocardial infarction or other injury can lead to lethal consequences. The current proposal will develop conditioned stem cell-derived cardiomyocyte that is resistant to cell death, leading to enhanced stem cell survival and retention for cardiac transplantation.
Funds Requested	$1,414,749
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	78
Median	80
Standard Deviation	4
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. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 6	• The study aims at heart failure, a common cause of death and currently not treatable (except heart transplants). The applicant wants to use human stem cells, differentiate them into cardiac myocytes (CM), and transplant them into the heart muscle. Several studies have already attempted this in animal models, including mice and pigs. Also, such pluripotent stem cell-derived heart cells are used in clinical studies for end-stage heart failure. • Stem cell-derived cardiomyocytes have significant potential in the treatment of heart failure. Better methods to enhance engraftment and survival in the damaged myocardium would help these cells meet their clinical promise. • A major problem, however that the majority of cardiac cells undergo cell death shortly after transplantation. The applicant hypothesizes that a specific pathway causes the formation of the so-called inflammasome that results in a form of apoptosis. • The proposed treatment is a potentially powerful approach to engineer the CMs to survive in a stressed environment after transplantation. • It isn't clear that inflammasome is the key mediator of CM death. Suppression of short-term inflammatory responses may not impact long-term survival in a meaningful manner.
No: 4	• Impressive improved survival but therapeutic application may be challenging. • The proposed activities will likely have a low impact.
GWG Votes	**Is the rationale sound?**
Yes: 7	• Mechanism should be investigated more in depth.
No: 3	• The team has preliminary data illustrating anti-inflammatory small molecule treatment of stem cell derived CMs increases their engraftment and improves functional outcomes in a mouse ischemia-reperfusion model. • The reliance on molecules and no clear delineation between blocker purpose and molecules dampen my enthusiasm. In addition, how much of an impact the inflammation blocking will have beyond 2-fold is not apparent. • The team has interesting preliminary data using small molecules to inhibit inflammation. The advantages of the proposed molecules vs. small molecules aren't explicitly stated. • Targeting the inflammasome addresses short-term survival but long term ischemia remains a barrier to CM survival.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 8	• If successful the project would demonstrate improved engraftment by stem cell derived CMs expressing molecules that target the inflammasome. This would motivate further study in larger animal models that are suited to functional improvements by the cells. • The experimental design is appropriate, and the group focuses on many of the details that will be later necessary for a successful clinical trial. • The project is well-designed to move from discovery of the candidate to evaluation of the cells in a mouse model. • The experiments are well-designed to identify molecular mechanisms of cell death in CMs in vitro. • The use of transcriptomics and bioinformatics to predict molecules that inhibit the inflammasome is well-designed. • Bioluminescent imaging to track cells through time after transplantation is a strength of the approach.

	• Experiment design and analysis are rigorous. • The mouse model is not well suited for effects of stem cell derived CM on regeneration since the human cells cannot match the mouse heart pacing. Paracrine effects may be seen but electromechanical coupling is not achievable. • The lack of in vitro evaluation of the molecules on CMs may slow progress.
No: 2	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 8	• The milestones were logical and represented the progress from validation to functional studies. It will be feasible, and this is a critical look at the transplantation, as they will look at inflammasome activity in detail. • The milestones are detailed and well-aligned with the goals of the proposal. • The team has complementary expertise and a strong history of collaboration, including on a prior CIRM funded project. • Success criteria are qualitative in nature. They address improvements, but not the magnitudes of these improvements that would make meaningful clinical impact.
No: 2	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 10	• The project is diverse, and attempts to include gender and ethnic backgrounds. The project addresses a critical need in California. • The project will use stem cells from male and female donors of three races. Only molecules upregulated in all lines will be chosen for analysis.
No: 0	*none*

Application #	DISC2-12610
Title (as written by the applicant)	Meniscal Repair and Regeneration
Research Objective (as written by the applicant)	Stem cells are seeded into fibers spun out of collagen to fabricate tissue that resembles the knee meniscus
Impact (as written by the applicant)	Meniscal tears are very common but do not heal. The treatment is removal of the torn tissue, which leads to osteoarthritis. If successful, replacing the tissue will prevent osteoarthritis.
Major Proposed Activities (as written by the applicant)	• Establish the identity and purity of the stem cells • Show proof of tissue regeneration in laboratory experiments • Show proof of meniscus regeneration in live animals • Conduct INTERACT meeting with the FDA to discuss the preclinical studies needed before clinical trials
Statement of Benefit to California (as written by the applicant)	Annually, over 100,000 Californians sustain meniscal injuries, the majority of which result in surgery for removal of damaged tissue. These injuries accelerate the early development of osteoarthritis, for which there is no effective treatment, other than total joint replacement, which is a major operation. There are significant socioeconomic benefits to preventing disabling osteoarthritis. The reductions in healthcare costs are also likely to be significant.
Funds Requested	$1,619,109
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	80
Lowest	62
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. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 10	• The annual incidence of meniscal injuries in the US is ~750,000 with 90% resulting in meniscal surgery. This is an important problem. • Meniscal tear is a common injury for which there is no adequate treatment except for the minority of cases where the tear is in the vascularised outer third of the meniscus (red zone tears). For the majority of tears, in the unvascularized, white zone, the standard of care is partial meniscectomy. This removal of the damaged tissue produces good short-term outcomes but poor long-term outcomes, with the frequent development of osteoarthritis. • The proposed technology will attempt to replace the meniscal tissue removed at meniscectomy, using a combination of scaffold, stem cell-derived meniscal progenitors and growth factor embedded in the scaffold. This would be a tissue engineering alternative to allograft (meniscus from donors) or cell-free artificial scaffolds. • Applicants propose to develop a biomimetic scaffold seeded with differentiated meniscal progenitors that proliferate locally and secrete matrix components that integrate into the scaffold, a significant improvement over the current standard of care. • If successful, the approach would result in a clear candidate for clinical development and for the treatment of an unmet need.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 8	• The basic rationale is sound.
No: 2	• There are several concerns with the proposed project. The phenotype of the cells is a concern. Evidence is provided for expression of cell surface proteins that are indicative of a stem cell phenotype, but no data provided on their propensity for driving calcification or for their multi-potential differentiation to cartilage/bone/adipose. This should be a standard for defining stem cells or equivalent precursors. And none of the preliminary data are provided for the GMP grade cell line that has been chosen for use; they have used Wisconsin H9 cells experimentally. • The quality of the derived meniscus forming cells is a concern. The background data in the paper do not address this and the cited paper only has data on hyaline cartilage formation, not meniscal cartilage. The preliminary data in the application only shows meniscal repair in vitro using mesenchymal stem cells, not the proposed precursors. • There is a lack of data on avoiding immune rejection. There are no data in the application itself and the cited paper referred to appears to have no data on immune rejection. Reference is made to the fact that clinical experience has shown that meniscal allografts are never rejected. This is true, but these allografts have no living cells (they are repopulated after implantation) and so provide no evidence in relation to cell implants. • Preliminary data specifically demonstrating that progenitors derived from the proposed cell line can avoid immune rejection when implanted into meniscal tissue are essential. This needs to be shown in the application itself as supporting background data. • The preliminary data that have been provided are not extensive and the figure legends are short and uninformative, making it difficult to interpret.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 3	• Aim 1 is proof of concept, including expansion of the proposed cell line, optimization of tissue engineering in vitro and of ex vivo meniscal regeneration. The meniscal regeneration will be analyzed by immunohistochemistry (for quality of the repair tissue) and mechanically (for stability of the neo-tissue). Success will be determined as neo-tissue assessed by histologic stains as well as mechanical testing with tensile properties greater than 100 MPa. The rationale for selection 100MPA as the minimum for

	mechanical strength has not been explained. The immunohistochemistry will provide useful information but will not provide a useful quantitative endpoint. The aim is to choose a lead candidate and one alternate candidate in terms of construct design. ● Aim 2 is in vivo proof of concept in a mouse atopic model and a rabbit meniscal injury model. The atopic model will assess tissue formation and safety. This model will involve xenogeneic implantation of human cells in nude mice. The rabbit model will also be xenogeneic but the rabbit will have an intact immune system and no immunosuppression will be used. The applicants refer to preliminary experiments indicating no immune rejection but the cited reference does not appear to include the relevant data and so it remains unclear if the experimental approach is viable. These data need to be described in the proposal itself. ● Work will be done in preparation for a sheep implant model although sheep studies will not be undertaken as part of this project. The final activity under the project will be an FDA INTERACT meeting that will help with translation of the findings into a clinical protocol.
No: 7	● Choice of cell lines should be justified better for translational aims. ● "Mann-Whitney test for pair-wise comparisons between groups with Bonferroni correction." Bonferroni is typically used for multiple test correction of independent tests. It isn't clear how many different independent tests are being done. Some more careful consideration of statistical significance and interpretation may be warranted. It is not sufficient to state "conservatism" as a rationale as such conservatism wastes power and resources (including animals, which bears on ethics). ● "Non-patentable intellectual property and communications with the FDA may be maintained as proprietary trade secrets." Why not share such information broadly? If receiving government funding at a non-profit (i.e., indirectly supported by the government) institution, what is the public interest in keeping such knowledge guarded? ● "fda" is generally capitalized as "FDA"
GWG Votes	**Is the proposal feasible?**
Yes: 7	● No concerns.
No: 3	● Applicants have not adequately addressed the issue of immune rejection. ● Feasibility depends on quality of the cell differentiation pathway and on the assumption that allogeneic/xenogeneic transplantation is possible in the absence of immune suppression. Evidence for this is lacking in the proposal as written and that makes this a high risk project. ● Convincing preliminary data on cell differentiation to MSCs/meniscocytes and on their survival in an allogeneic/xenogeenic implantation without immunosuppression are essential in order properly to assess feasibility.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 10	● This is a generally applicable tool. ● Meniscal tear affects all communities and so new repair methods will be available to a diverse population.
No: 0	*none*

Application #	DISC2-12544
Title (as written by the applicant)	A synergistic stem cell and gene therapy for glaucoma
Research Objective (as written by the applicant)	A combined stem cell and gene therapy will be delivered to the site of disease to protect retinal ganglion cells (RGCs) from secondary degeneration in glaucoma.
Impact (as written by the applicant)	This approach of targeting the site of disease with a clinically-validated stem cell and gene therapy can be translated into clinical trial for treating patients with glaucoma.
Major Proposed Activities (as written by the applicant)	• 1) Characterization of hNPC-GDNF in vitro including neural progenitor cell markers and GDNF secretion 2) Validate rat model for glaucoma by bead occlusion with our published protocol • 1) Deliver hNPC-GDNF to the ONH at early stage of disease , check visual function and histology 2) Deliver hNPC-GDNF to the ONH at later stage of disease. check visual function and Histology. • 1) A rang of doses will be tested for dose escalation study (20K to 120K) at early stage of disease 2) Identify the optimal dose (Minimum cell dose that offers the best efficacy) • 1) Gene expression study by spatial transcriptomic after hNPC-GDNF delivered to the ONH. 2) Direct comparation between cell-and control-treated, and between early-and later-stages of glaucoma.
Statement of Benefit to California (as written by the applicant)	This project involves developing a novel treatment for glaucoma, the second leading cause of blindness in the world. Firstly, the project itself will employ new administrative, scientific personnel in California . Secondly, the development of this stem cell based drug ensure that the state retains its lead in the commercialization of stem cell technologies. Thirdly, if successful, this treatment would provide a substantial improvement to Californians who are suffering from glaucoma.
Funds Requested	$1,353,283
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	1
Highest	79
Lowest	75

Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 7	• Glaucoma is a serious problem for which new treatments are very much needed. • High unmet need, already approved cell product. • GMP cell product already in clinical trials. • They have a GMP cell line ready to go that has shown safety in humans in a clinical phase 1 ALS trial. They have demonstrated safety and tolerability with this cell line in humans and cell integration. I like the dose ranging aspect. • The proposal is based on the site of injury being at the optic nerve and being primarily due to astrocytes. This may not be the true picture in an age related glaucomatous process which is multifactorial. • Although not directly translatable with an optic nerve injection, if it can be delivered via intravitreal, this could have potential. • Transplant in the optic nerve is not justified • Major concern is the surgical intervention approach. This will never be commercially acceptable for a slowly progressive asymptomatic disease. • Timing of intervention in clinical translation is a weakness.
No: 3	• Novel. Exciting innovative concept. • Not clear there is a path to widespread clinical adoption. • There is low translational potential.
GWG Votes	**Is the rationale sound?**
Yes: 4	• Again the assumption that this is purely a disease of astrocytes is limited. The use of glial progenitor cells with delivery of neurotrophic factors does make sense.
No: 6	• Only in part. For example, there is no evidence that injection of cells into the optic nerve head will provide protection (or trophic factor delivery) to the RGCs. • The idea that patients will agree to cell injections at the early stages of glaucoma seems unlikely, and the evidence that this would matter at later stages does not exist. • Glaucoma is a condition that develops over a long time, whereas this is an acute intervention. Thus, the proposed experiments do not model the disease. • Rationale of transplantation into the optic nerve head is not provided, limited preliminary data.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 8	• It's scientifically well designed, but has problems in terms of clinical development. • Except for only injecting into the optic nerve. The model is acceptable. • The visual function assessments may not show anything given this model may not have rapid central visual loss and we do not routinely use ERG for glaucoma.
No: 2	• Disease is highly chronic but gene dose is applied acutely - this problem is not addressed.

GWG Votes	Is the proposal feasible?
Yes: 6	• Yes - the timeframe, PI expertise and resources needed are reasonable. It can advance the field if positive.
No: 3	• They are able to do the experiments proposed. But there are experiments lacking (e.g., vitreous transplants, delayed transplants). • In terms of developing a therapy, it doesn't seem feasible. • Technically yes as a proof of concept but leap to a translational product is nearly insurmountable. • Questions about functional readout in rats.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 9	• Glaucoma is an under-recognized disease in the lower socioeconomic classes and a major cause of blindness worldwide. Latinos and African Americans also suffer from this debilitating disease at an earlier age. • Glaucoma is a serious problem in underserved communities.
No: 1	*none*

Application #	DISC2-12690
Title (as written by the applicant)	Pro-angiogenic nanotechnology for neural stem cell transplantation after stroke
Research Objective (as written by the applicant)	We propose to develop an injectable soft material that can encapsulate brain cells and promote their long-term survival through blood perfusion to repair the brain after stroke
Impact (as written by the applicant)	If the proposed study is successfully achieved, we will have developed a nanotechnology-based stem cell therapy that enhances cell survival and integration in the brain after transplantation
Major Proposed Activities (as written by the applicant)	• Fabrication of the engineered material • Generation of the neural stem cells • Encapsulation of neural stem cells in the material and brain injection in the stroke lesion • Evaluation of brain inflammation and cell survival • Evaluation of vessel formation • Evaluation of tissue repair and recovery of neurological deficit
Statement of Benefit to California (as written by the applicant)	The proposed research will benefit the State of California and its large population of diverse ethnicity, gender, age, and socioeconomic status.
Funds Requested	$1,444,500
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 75

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

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

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 8	• Stroke is an enormous problem with no effective therapeutic approach to prevent damage. • Affects a large population and is more prevalent among undeserved communities. • Neural stem cell (NSC) transplantation in the brain after stroke could benefit patients and promote functional improvement. • NSC survival and pro-regenerative potential after transplantation in the stroke cavity of the brain can be enhanced by cell delivery through hydrogels and by including pro-angiogenic factors. • High cost for patient care. • Therapies only work in a small window post stroke. • A discussion on clinical applicability of the chosen progenitor cells and hydrogels is missing
No: 2	*none*
GWG Votes	**Is the rationale sound?**
Yes: 4	• No concerns.
No: 6	• Biomaterial alone provides already near complete recovery (published previously), no good reason to include poorly defined stem cells. • Formulation of hydrogel to maximize NSC survival in vitro and in vivo after injection in the mouse stroke cavity has been identified. However it is not clear if the hydrogel with the highest growth factors also improves functional outcomes. • Formulation of pro-angiogenic hydrogel to maximize angiogenesis, axonal sprouting, and functional recovery through behavior tests after injection in the mouse stroke cavity has been identifiedd. However, the formulation of the pro-angiogenic gels has not been justified. • Hydrogel optimization is confusing. • For human NSC transplantation studies in mice there is no mention of immunosuppression used, if any.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 5	• Gel composition and NSC differentiation were previously optimized and available for testing. • Experimental methods for testing combination product in a mouse model of stroke are available. • Some preliminary data are missing details; alternative strategies are poorly described; in vitro studies before in vivo testing are missing. • Xenotransplantation of human NSCs in immunocompetent mice will likely be more challenging than expected. • Potential pitfalls and alternative strategies are discussed, however the section is minimal and could be improved.
No: 5	• The preliminary data was not compelling enough for the proposed plan. • No rationale for the 5 day injection time point. • Issues of size of stroke area are not addressed. • Cell source and consistency are not addressed-stem cell, neurons? • Immune rejection issues are not addressed. • Stroke area need to be clearly defined, how will cells be targeted correctly? • Incremental advance from previous work.

	• How is the glial scar overcome? • Control of proliferation and differentiation is not apparent.
GWG Votes	**Is the proposal feasible?**
Yes: 8	• Milestones are clear and achievable. • Adequate resources and budget. • Parts of the work have been done before. • No milestone is provided for testing the cortical progenitor cells in the hydrogel in vitro before in vivo studies.
No: 2	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 10	• Applicant uses chronic model of stroke and aged mice, relevant to human aged stroke. • Inclusion of male and female mice. • Both male and female mice will be used. • Clinical studies will be associated with inclusion of populations of diverse race or ethnicity, gender, age, and socioeconomic status. • Statistics on disparity between socio-economical statuses and ethnicity in stroke patients is provided. • There is no discussion on diversity, equity and inclusion considerations in the research team.
No: 0	*none*

Application #	DISC2-12678
Title (as written by the applicant)	Development of monothiol human thioredoxin-1 (ORP100S) as an inhaled treatment for COVID-19 respiratory disease
Research Objective (as written by the applicant)	We want to investigate if ORP100S can be used as therapeutic drugs against SARS-CoV-2-induced cytokine storm on alveolar epithelial type 2 cells, the stem cells in the lung.
Impact (as written by the applicant)	This would validate the ORP100S as a potential treatment against SRAS-CoV-2-induced cytokine dysregulation.
Major Proposed Activities (as written by the applicant)	• Efficacy study to evaluate the dose response of ORP100S to modulate pro-inflammatory cytokine release using SARS-CoV-2 live virus-infected hPSC-lung organoids. • Determine the effects of ORP100S on the production of pro-inflammatory cytokines by normal human bronchial epithelial cells (HBEs) following bleomycin-induced inflammatory stimulus. • Test ORP-100S pharmacodynamic effect in a hamster model of SARS CoV-2 infection.
Statement of Benefit to California (as written by the applicant)	The proposed research will provide a potential treatment for patients who suffers from elevated cytokine levels due to the SARS-CoV-2 infection. Completion of the proposed research will benefit the State of California and its citizens enable Californians to live without social distancing requirements.
Funds Requested	$1,125,940
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 75

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

Mean	75
Median	75
Standard Deviation	4
Highest	90
Lowest	70
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. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 8	• The investigators have proposed to examine an anti-inflammatory approach to interrupt the development of inflammation and compromise in lung function resulting in acute respiratory distress in COVID-19. The approach is similar in effect to one that has been developed and commercialized by other investigators and has been shown to be capable of interrupting the acute cytokine storm that results in influenza infections. • Stem cells are the figurative Canary in the Coal mine in these studies. The AT2 cell is a critical cell in the function of the alveolus, and the goal with the candidate is to preserve the AT2 cells as the precursor cell for alveolar regeneration. The effect is not likely to have an antiviral component, but to mitigate damage to these critical cells. • The overall idea is valid but the lack of preliminary data makes it difficult to judge the impact. • Because the redox balance is important for cell-cell signaling, ligand receptor interaction, there is some concern on secondary effects.
No: 4	• Effects may not be specific since there is no targeting.
GWG Votes	**Is the rationale sound?**
Yes: 7	• The modification of TRDX1 is potentially important, increasing the extracellular activity. • Yes, in general but little discussion of data that would allow insight into mechanism.
No: 5	• Complex reasoning that requires a number of assumptions to be applied, but a very detailed experimental plan. • Preliminary data in preclinical models are missing. • The preliminary data is interesting, but the numbers of iterations and the selection of factors to be quantitated appears to be in flux and may be expanded. This was particularly evident in the selection of cytokines, chemokine and acute phase reactants that would be followed. • The stem cells are not used well in the proposal.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 8	• Detailed protocol but lacks in discussion of pitfalls. • Impact on inflammation is not shown. • No concerns are noted.
No: 4	• This is a very detailed proposal by a competent group of investigators. The proposed experiments targeting the AT2 cells are worthwhile, but their importance to the field of stem cell biology is less clear. • It is a detailed, workman-like effort by a competent group of professionals. That said it is an effort to develop the and test the drug ORP-100S. That goal often feels like the primary goal of the research. • Include more inflammatory models to demonstrate the efficacy of the modified compound. • in vitro systems without immune cells may not be the right model for testing. • Alternative strategies and potential pitfalls are missing. • Pitfalls are not discussed in any real detail.
GWG Votes	**Is the proposal feasible?**
Yes: 10	• The proposed experiments are feasible, there is some moderate concern in the clinical relevance of the observations. Multiple trials have been conducted with anti-oxidants with moderated or negative results. • Detailed. • The project will likely require more than the one year time frame that is proposed.

No: 2	• No evidence that compound has same anti-inflammatory effects on SARS.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 11	• Covid-19 is more prevalent in underserved communities. • The applicant has not specified how patients will be enrolled for cell collection.
No: 1	• Recruitment of minority patients is not discussed. • The project presents two lines of involvement of URM. 1) samples of lung cells will be obtained from all of the major URM groups. 2) what appears to be an educational component involving URM children will be undertaken. Details are not provided for either activity. • If the strategy is successful and if it works to suppress the pathogenic effects of other respiratory viruses beyond SARS-CoV-2, then it will be valuable to the CA population.

Application #	DISC2-12644
Title (as written by the applicant)	Extending Immune-Evasive Human Islet-Like Organoids (HILOs) Survival and Function as a Cure for T1D
Research Objective (as written by the applicant)	Determine optimal islet transplant conditions and systemic treatments that promote graft survival upon transplantation into immune-competent diabetic subjects.
Impact (as written by the applicant)	Our proposal will optimize the generation and viability of an unlimited, reproducible source of human engineered islets for transplantation.
Major Proposed Activities (as written by the applicant)	• Demonstrate improved HILO graft survival with FGF1 coating • Prolong grafted HILO survival by reducing metabolic insulin demand • Enhance capillary formation in the immediate area of transplanted beta-cells in HILOs with novel GLP1-FGF1 conjugate
Statement of Benefit to California (as written by the applicant)	Diabetes affects 3 million people in California. Type 1 diabetes is a particular burden as it requires life-long administration of insulin. Allo-transplantation of islets is limited by availability of donor cells. This proposal will facilitate the generation of functional ESC-derived islet-like organoids as an unlimited, reproducible source and optimize methods to increase functionality and viability upon transplantation into diabetic patients.
Funds Requested	$1,543,562
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 75

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

Mean	75
Median	75
Standard Deviation	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. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 11	• The proposed technology aims to enhance integration of pluripotent stem cell-derived islet-like organoids to improve their utility in treating type 1 diabetes. These HILOs have significant potential as a candidate cell therapy to treat T1D and improving integration/viability is a logical step in candidate development. • Human islet-like organoids (HILOs) from stem cell source with improved functionality, immunoevasive properties and insulin-boosting pro-angiogenic effects could address main challenges associated with beta cell replacement in T1D. • SC-derived islets still require chronic immunosuppression to prevent rejection and recurrence of autoimmunity and strategies to improve engraftment in clinically-applicable sites to reduce dosing and improve functionality as metabolic control is a strength. • The proposal is addressing a key road block in diabetes by reducing metabolic stress. • Potential high risk-high reward. • There is a mention that translational funding opportunities will be pursued in the future.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 8	• The candidate is complex, consisting of the HILO with various types of molecular treatments prior to and after administration. The complexity may complicate translation but the use of FGF1 in conjunction with other treatments to induce vascularization and reduce metabolic stresses is warranted. • Publications and preliminary data by this group establish the development of functionally mature HILOs from hESCs and the use of these to control glucose in diabetic mouse models. • Preliminary data suggest a role for FGF1 in neovascularization and glucose regulation. The glucose regulation is insulin-dependent but does not require beta cells, suggesting it is appropriate for complementing nascent beta cells. • Adding growth factors could be beneficial.
No: 3	• Achieving functional maturation of SC-islets in vitro remains a challenge. Treated HILOs show improved glucose-stimulated insulin secretion and restore glucose homeostasis in diabetic mice with similar efficacy to human islets but blood glucose levels are not normal. • Immune-evasive HILOs display prolonged efficacy when transplanted into immune-competent mice. • Preliminary data show FGF1 is a key metabolic regulator of glucose homeostasis and glucose lowering effect of FGF1 is dependent on adipose FGFR1 signaling. • Treated HILOs show, in vitro, higher glucose-stimulated insulin secretion index during transition than HILOs and in vivo functionality comparable to human islets in the kidney capsule of mice. • Data shown in Fig.1B show increased c-peptide section after stimulation but do not show insulin shutdown after transition; KCl stimulation did not increase c-peptide secretion as it normally occurs with human islets and may indicate deficient insulin secretion of HILOs. • Blood glucose of immunocompetent mice receiving treated HILOs is not normal; it's not discussed whether this is due to low dose or partial graft rejection. • The in vivo studies were performed in the kidney capsule which is a site that minimizes graft hypoxia and is not clinically translatable. • GLP1-FGF1 synthetic hormone demonstrates effective beta cell targeting. However data shown in Fig.6 do not demonstrate statistically significant effects of GLP1-FGF1 in targeting beta cells and lowering blood glucose values compared to unmodified FGF1.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 8	• The objectives are logically organized to evaluate the role of FGF1 in improving HILO viability via vascularization and reducing metabolic stress.

	• Use of the humanized mouse model is an appropriate way to develop the technology at this point. • Imaging of vascularization will allow the investigators to test their hypothesis in objective 1. • Use of single cell RNA sequencing is a good way to evaluate the effects of various treatment on cell states. Feasibility of single cell RNAseq in explanted HILOs should be supported by preliminary data. • Experiment design is high level and lacks the expected rigor. Details about controls, sample sizes, data analysis are not provided. • Delivery is considered but molecular localization is not effectively investigated or systematically varied. • Lack of convincing data on pro-angiogenic potential and targeting of GLP1-FGF1. • The investigators consider potential off-target effects of FGF1, although at a systemic level these will be difficult to identify and may represent a safety issue for translation.. • Very ambitious plan to test improved protocol for HILO-FGF1 transplantation in kidney capsule of humanized mice. • Treatment with pro-angiogenic factors may not show beneficial effects when HILOs are transplanted in the kidney capsule which is known to be more favorable to islet engraftment than other clinically-applicable sites. • For milestone 2, 6 month follow up in humanized mice may not be possible due to GVHD. • Details on how inflammatory signals will be monitored in the grafts are not provided. • Very nice discussion on potential pitfalls. However, alternative approaches are very ambitious and missing experimental details and expertise. Alternative sites are mentioned briefly with no feasibility data; PLGA delivery of pro-angiogenic factors is mentioned but without any details (loading needs to be done in situ).
No: 3	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 8	• This team is outstanding. They are a leader in developing hESC-based therapies to treat T1D. • The milestones are well-aligned with project translational goals but seem ambitious for a two year project • Success criteria are quantitative. Some goals seem modest and not sufficient to overcome roadblock to translation. • The aims are too ambitious, given the state of the preliminary data.
No: 3	• Highly overambitious, questions of feasibility, • Milestone 1 and 2 may be achievable. Milestone 3 does not have sufficient support and is overlapping. • PI team has the necessary expertise to make and test the HILOs in humanized mice. • Expertise in growth factor delivery, angiogenesis, graft assessment is missing. • Adequate resources. • Adequate budget.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 11	• T1D is a major, growing biomedical challenge for society and is particularly burdensome for underserved communities. • T1D statistics in underserved and low-income communities is provided; the therapeutic development of HILOs will provide superior disease management for these at-risk populations; cost estimates are provided. • Very nice discussion in Diversity, Equity and Inclusion in Research.
No: 0	*none*

Application #	DISC2-12380
Title (as written by the applicant)	A therapeutic antibody to promote macrophage-mediated killing of cancer stem cells
Research Objective (as written by the applicant)	A therapeutic antibody that exploits the tumor associated macrophages enriched in stem-like tumors to induce antibody-dependent cellular cytotoxicity for selective killing of cancer stem cells (CSC).
Impact (as written by the applicant)	Our antibody will treat epithelial-derived cancers such as those from the lung, breast, or pancreas that have become refractory to standard of care and become stem-like, mesenchymal, and immune-cold.
Major Proposed Activities (as written by the applicant)	• Generate new humanized monoclonal and bispecific antibodies that activate tumor associated macrophages and recognize one or two CSC markers, respectively. • Compare new antibodies to existing prototype antibody for ability to utilize macrophages to kill cancer stem cells in vitro. • Characterize anti-tumor efficacy for the top 3 candidates using lung cancer xenograft models in mice. • Select one lead candidate for full characterization of efficacy and mechanism of action in a syngeneic mouse tumor model expressing human αvβ3. • Delivery of therapeutic candidate.
Statement of Benefit to California (as written by the applicant)	Epithelial-derived cancers (such as those from the lung, breast, or pancreas) progress to become stem-like, mesenchymal, and immune-cold. Such tumors no longer respond to targeted therapeutics and immunotherapies designed to control the original epithelial cancer, and patients ultimately die from expansion of a pre-existing and/or induced cancer stem cell (CSC) population. By eliminating CSC, our antibody therapeutic will create a tumor that is more responsive to standard of care therapy.
Funds Requested	$1,425,546
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	2
Highest	75
Lowest	70
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 7	• The diseases that are studied can be lethal in advanced stages. • Cancer stem cell targeting agents are lacking. • Antibody already developed and available but not clear what were the issues with it in human trials.
No: 3	*none*
GWG Votes	**Is the rationale sound?**
Yes: 5	• No concerns.
No: 5	• The use of this targeting agent has been safe. • The data regarding the integrin as a CSC antigen is reasonable. • It is not clear why the previous product failed in clinical trials. • There is no data from the clinical trial what the mechanisms of failure are. Why do they think that it was due to effector cells? • The application seems not to be informed by their previous work. • Heterogeneity of cancer stem cells not discussed.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 4	• The steps to product development are reasonable. • None of their assays test CSC function. • Wrong assays for analyzing tumor stem cells.
No: 6	• Lack of cancer stem cell assays is a weakness. • Secondary tumor transplants should be proposed.
GWG Votes	**Is the proposal feasible?**
Yes: 7	• The proposal is feasible based on the previous work of the investigators. • PI is overfunded (>100% effort covered).
No: 3	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 10	• Yes.
No: 0	*none*

Application #	DISC2-12486
Title (as written by the applicant)	A BioMEMS platform for multiplexed, non-viral nuclear delivery of biomolecules into human stem cells using surface-functionalized silicon nanoneedles
Research Objective (as written by the applicant)	To develop a scalable BioMEMS tool for the delivery of biomolecules into human stem cells using MEMS-actuated, surface-functionalized nanoneedles.
Impact (as written by the applicant)	The proposed platform for efficient delivery of biomolecules into stem cells can significantly advance research and therapeutics and make these therapies more accessible to the general population.
Major Proposed Activities (as written by the applicant)	• Build and optimize BioMEMS tool subcomponents for stem cell handling. • Validate delivery mechanisms with mRNA inserted into living cells using the BioMEMS components. • Integrate BioMEMS subcomponents and assemble a benchtop prototype of the BioMEMS tool. • Demonstrate ratiometric, multiplexed mRNA delivery with the benchtop platform. Using these features, reprogram fibroblast cells into iPS cells by delivery of mRNA expressing Yamanaka factors.
Statement of Benefit to California (as written by the applicant)	Stem cell therapies can be potential cures for a variety of diseases, including diseases such as cancer and diabetes (the 2nd and 7th leading cause of death) that are prevalent in residents of California. Developing a platform that can make stem cell therapies more accessible can directly benefit the population. All the research being done here is performed by California residents in facilities located in the bay area.
Funds Requested	$495,460
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	7
Highest	80
Lowest	50
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. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 6	• There is an urgency and need for new technologies to deliver biomolecules to stem cells. This proposal directly addresses that need. Improved delivery of biomolecules and nucleic acids to cells could ameliorate a bottleneck in stem cell technologies, and possibly open up new ways to manipulate cells, leading to better stem cell therapies. • "Rationale: After demonstrating the ability of our system to deliver DNA plasmids into stem cells, the ability of our system to be able to deliver other nucleic acids would broaden the applications of the technology. Furthermore, comparing our technology with an existing approach will show a direct improvement of our platform over existing methods." Applicants need to be more specific about examples of specific applications that would be enabled by this technology.
No: 4	• Potential application and superiority of the technology is missing.
GWG Votes	**Is the rationale sound?**
Yes: 8	• Need to do a thorough review of the competitive landscape. How does this technology stack up? What niche does it fill and/or what advantages does it have over all other technologies? For example, there are microfluidic techniques that perform purification through tiny pores. Are they faster? Do they do less damage to cells?
No: 2	• The system is over-engineered and needs more biological focus.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 3	• No concerns.
No: 7	• Is lipofectamine the only other delivery mechanism? Is it the best straw dummy? They state that they will use lipofectamine as their control or straw-dummy to compare the effectiveness of their new device for transfection efficiency. However, this is a bit vague. It is important to compare to the best state-of-the-art method. For example, there are at least three lipofectamine protocols based on lipofectamine-2000 (Lipo2K), lipofectamine-3000 (Lipo3K), and Lipofectamine STEM (LipoSTEM). • Some of the scientific advisors to the company have a lot of experience in writing grants. It may be helpful to ask the scientific advisors of the company to provide advice on how to instill rigor and detail into this grant application. • The PI has experience in stem cell production. Other than that, it is not clear if this lab routinely generates stem cells. They mention access to a research institute, but it is unclear if they have turnkey ability to produce the stem cells necessary for testing this project.
GWG Votes	**Is the proposal feasible?**
Yes: 9	• The project is straightforward.
No: 1	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 10	• This is a general tool with broad applicability.
No: 0	*none*

Application #	DISC2-12312
Title (as written by the applicant)	A human pre-implantation embryo tool to discover mechanisms and therapies for rare genetic diseases
Research Objective (as written by the applicant)	The objective of this proposal is to develop stem cell-based models of the human pre-implantation embryo (blastoids) that serve as a drug discovery tool for rare genetic diseases.
Impact (as written by the applicant)	Human blastoids can be genetically modified to generate much-needed models of rare diseases to decipher pathological mechanisms and identify potential therapeutics by high-throughput drug screening.
Major Proposed Activities (as written by the applicant)	• Derive human blastoids in vitro from (i) human extended pluripotent cells (hEPSCs), (ii) hEPSCs and human trophoblast stem cells, and (ii) genetically modified naïve embryonic stem cells. • Develop human blastoids beyond implantation in vitro. • Generate human blastoid models of rare disease using CRISPR-Cas9 technology. • Identify potential therapeutics via high-throughput screening of human blastoid rare disease models with a library of FDA-approved drugs.
Statement of Benefit to California (as written by the applicant)	The National Organization for Rare Disease estimates that ~25 million Americans suffer from a rare disease, 4 million of which live in California. Additionally, 90% of these "orphan diseases" remain untreated. Our study aims to develop a stem cell model of the human pre-implantation embryo that will serve as a drug discovery tool for rare genetic diseases. This tool will drastically lower the time and cost necessary to develop novel therapeutics to the benefit of California and its citizens.
Funds Requested	$590,100
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 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	8
Highest	85
Lowest	60
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. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 8	• Yes. "Rare" diseases are actually quite common. Each individual disease is rare, but in aggregate they are common. Stem cell technologies are a major hope for individualizing treatment and enabling research on rare diseases. These diseases tend to be underfunded in general, so this proposal fits perfectly with CIRM's mission. • Stand-ins for pre-implantation embryos that have introduced variants corresponding to rare human diseases could advance understanding of these diseases and provide a platform for screening drugs to treat these diseases. • This grant would create "blastoid" models of 3 rare human monogenic disorders that would allow the study of early embryonic aspects of disease mechanisms. "Blastoids" (which are somewhat similar to embryoid bodies) will be derived from human extended pluripotent stem cells (hEPSCs) which have the capacity to form blastocyst-like embryoid structures that model blastocyst and very early post-implantation stages. These blastoids can model aspects of preimplantion and early post-implantation embryology including establishment of germ layers, gastrulation, and formation of extra-embryonic tissues. • The concept of progression to a successful candidate is sound in theory: Create mutant pluripotent cells and blastoids, find markers of early development that are perturbed by the mutation, and then find compounds that correct the developmental defect. However, the likelihood of finding such a compound is not strong, as early differentiated blastocysts may not exhibit phenotypes that are clinically relevant at this very early developmental stage (this is a major weakness), the GFP reporters for screen are not yet designed, and the compound library proposed contains only less than 200 compounds. • The compound screen proposed is of very limited scope and there is a significant likelihood that no compounds will be found that can impact the course of very early developmental modeling, even in knockout pluripotent EBs (blastoids). • Many diseases (neurological) cannot be diagnosed at such an early developmental stage. • Not clearly stated, translation to clinic not obvious.
No: 2	• The work is unlikely to produce a therapeutic at the end of two years. The utility of any blastoid tool is also unclear.
GWG Votes	**Is the rationale sound?**
Yes: 4	• The preliminary data is strong. The basic protocol for blastoid development is established. • The major flaw in the proposal is the "high throughput" screening aim. "We will perform a high-throughput screen with[...] the Tocriscreen FDA-Approved Drugs Library, a library of 190 compounds." This is a shotgun approach with a very small shotgun. The likelihood of any of these drugs specifically treating the genetic defect(s) in question is small. You need a much bigger shotgun or a rifle. Given limitations on throughput, a rifle is needed. Select several dozen compounds specifically selected as likely to treat the specific gene in question and screen those. • Collaborate with drug-repurposing theoreticians if necessary to select likely candidates. • "We expect that treatment with one of the 190 FDA-approved drugs will restore proper marker expression..." Provide justification for this expectation. Are you arguing that all diseases can be treated by at least one of these 190 drugs?
No: 6	• Overall yes, though the technology used is very similar to simply producing embryoid bodies by aggregation, but this group has taken this approach to a new level in which early post implantation development is successfully modeled. • No consideration for maternal impact, placental transfer. • No data that would suggest that the early time point is relevant.

	• More thought on the translation of the drug in relation to infertility and the genetic diagnosis needs to be provided. • The developmental window may be very early for many disorders, and the technology should be demonstrated with a single gene or disease at least.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 4	• Drug screen is a poorly developed approach.
No: 6	• The notion that a drug capable of treating one of the 3 early developmental defects caused by mutation of one of the 3 genes proposed is fairly remote, though the research plan is logical. • The project is not very novel, and suffers from a very limited scope. Only 3 or 4 mutations will be assessed, phenotypes may or may not manifest, and the compound library to be screened is very small. • A major pitfall is identified that none of the 3 genes (when disrupted by CRISPR) will exhibit a very early developmental defect (as the assay can only detect defects up to the peri-implantation stage using a limited set of markers). The alternative approach is simply to try another of the many hundreds of other embryonic lethal genes should these 3 not work out. • The proposal is a bit linear, e.g., If all of the introduced mutations are lethal, alternative approaches are only vaguely described. • Pitfalls address mostly non-catastrophic pitfalls. What if one step fails completely? It seems there may be some bigger pitfalls than have been considered and these should be acknowledge with plans to address them.
GWG Votes	**Is the proposal feasible?**
Yes: 6	• Data Sharing Plan is very vague. "Upon request" is an outdated approach to sharing. Data Sharing Plan needs to mention specific public databases. Are there some databases of drug-gene interactions that would be appropriate to deposit the 190 drugs x 3 genes tested? Perhaps at NCBI/NCATS? • The team may need more expertise. Seems to be lacking a bit on bioinformatics, particularly on computational predictions of drug efficacy.
No: 4	• A large measure of luck will be required to find a drug that can treat one of the three monogenic diseases proposed for study, should they fortuitously prove to exhibit an early developmental post-implantation phenotype. • Likelihood to identify a compound in the limited screen is low.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 9	• The project is adaptable to whatever populations bear mutations in the genes under study and will coincide with allele frequencies for rare monogenic disorders within specific ethnicities. • Yes, this is equally applicable to all communities. Indeed, individualized approaches such as this will help the inequity that exists from "one size fits all" approaches developed from European-centric research.
No: 1	• Population that would benefit is not defined.

Application #	DISC2-12412
Title (as written by the applicant)	Generation of safe beta-like cells from pluripotent stem cells for treating type 1 diabetes
Research Objective (as written by the applicant)	We propose to genetically modify human pluripotent stem cells (hPSCs) to produce safe beta-like cells that can be transplanted into type 1 diabetes (T1D) patients for treatment.
Impact (as written by the applicant)	Residue undifferentiated hPSC in beta-like cells and serotonin produced from some beta-like cells pose safety concern, and can be addressed by the proposed studies.
Major Proposed Activities (as written by the applicant)	• Establish a genetically modified stem cell line expressing a gene product that can eradicate residue hPSCs. The key gene for serotonin synthesis will also be inactivated in this cell line. • To expand our stem cell repertoire in preparing for clinical application, we will use the same genetic strategy as Activity 1 to establish a different stem cell line to produce beta-like cells. • As a backup for eradicating residue hPSCs, we will test an alternative protein product by inserting its gene into hPSCs. Evaluation of efficacy will be carried out both in culture and in animals.
Statement of Benefit to California (as written by the applicant)	Based on the study of T1D patients in US from 2001-2016, the prevalence rate in California is estimated to be 5.4 per 10,000 persons. T1D patients have medical expenses approximately 2.3 times higher than those who do not have diabetes. Islet transplantation is effective in treating T1D but is limited by the donor source. Stem cell-derived beta-like cells provide an unlimited supply of beta cells to cure T1D and relieve the huge financial burden to the state.
Funds Requested	$1,124,122
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	75
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. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 9	• This grant may produce two human pluripotent cell lines. Such cells when differentiated to beta cells might be used to treat type 1 diabetes. • A pair of useful cell lines will be produced that can be useful for allogenic engrafted cells to treat type 1 diabetes, though it is not entirely clear that this is a major advance over previous successes. The bottleneck addressed is not the production of beta cells from pluripotent cells, rather it is increased safety via use of suicide genes. • There is a need of increasing safety of stem cell-derived islets by reducing their tumorigenic potential and their serotonin secretion in cell products that are not fully differentiated while other research is focused on improving differentiation protocols. Stem cell derived islets will address a major shortcoming of clinical beta cell replacement therapies but safety is a concern; thus, genetic engineering of stem cells to address safety issues of potential tumorigenesis and serotonin secretion could increase their clinical applicability. • There is a mention of clinical studies but a discussion on the clinical applicability of the SC products developed is missing
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 5	• No concerns.
No: 5	• The grant contains strong preliminary data to show that cells are properly engineered and that beta cells can be produced by their differentiation. • Genetic engineering approach is validated by preliminary data. • Data showing establishment and differentiation of an iPSC line from MSCs are provided. • Proposed modifications are effective in killing undifferentiated stem cells. • The large majority of data are qualitative and not quantitative. • Derived S6 SC-islets show some functionality after transplantation in the kidney capsule of mice but their phenotypical characterization before and after transplantation is poor. • Phenotypic and functional analysis of hESC-derived S7 cells is provided but not adequately developed. • Characterization of hESC clone is provided but not adequately developed. • In vitro functionality of S6 SC-islets in vitro is missing. • Decreased cell viability after overnight treatment with the drug at the indicated concentration is demonstrated for undifferentiated hESC cells but not sure if the same response can be obtained on the rare tumorigenic cells in the S7 SC-islet product. • hESC-derived beta-like cells are resistant to drug treatment so it's not clear which tumorigenic cells, if any, of the final product will be targeted by the treatment. • No evidence that the S6 SC-islets develop tumors after transplantation and that the proposed genetic modifications will target those rare cells in S6 SC-islets that are the safety concern for transplantation. • Characterization of S7 SC-islets lacks single cell resolution to justify the proposed approach. • A significant drawback of this approach is that only allogenic beta cells will be produced, requiring life-long immunosuppression to maintain engrafted cells.

GWG Votes	Is the proposal well planned and designed?
Yes: 2	*none*
No: 8	• The grant may yield a pair of cell lines that might be differentiated to bulk beta cells sufficient in number to treat type 1 diabetes. • Genetic engineering approaches are well described and potential pitfalls and alternative strategies are discussed adequately. • The first suicide gene is likely only useful to rid cultures of undifferentiated cells, and the use of a second suicide gene to remove malignant cells is a sound idea. • Genome stability and off-target effects will be adequately studied. • One concern is that heavy CRISPR engineering might harm the pluripotent cell genome. The applicants will sequence cell lines to ascertain if damage (off target) has occurred, but the response is simply to then screen clones until undamaged ones are found. If most clones exhibit off-target damage, this may be a substantial roadblock. • Characterization of genetically engineered S6 islets is included but not supported by preliminary feasibility data. • The choice and characterization of cell lines need further study. • For some experiments the kidney capsule is used as transplant site while for others the subcutaneous site; the tumorigenic potential of the cells may be affected and should be tested in a clinically applicable site. • Utilization of pancreatic cancer cell lines as model of tumorigenic cells for transplantation studies is poorly justified and arguable. • The rationale for caution regarding overproduction of serotonin is not well presented. • Feasibility of knockout of the gene to inhibit serotonin production and its positive effects on improving safety and graft outcomes is not supported by preliminary data. • The allogenic nature of cells produced is a drawback. • Feasibility of establishing the back-up gene in Aim 2 is not supported by preliminary data. • It is not clear whether the drugs will be used for in vitro (before transplant) or in vivo treatment (after transplant). • The grant is poorly written with several grammatical errors and poor quality panels.
GWG Votes	**Is the proposal feasible?**
Yes: 6	• Yes, the plans are quite feasible and should be doable in the proposed timeline. • No concerns.
No: 4	• Yes, clear and feasible milestones. • PI will supervise two post docs and will interact with a collaborator for clinical translation. However, there is no mention on how the collaborator will help translate the cell product to the clinic. • Adequate resources and budget.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 10	• No concerns, though the deliverable will be used to treat type 1 diabetes regardless of race, ethnicity, and sex. • Very nice discussion.
No: 0	*none*

Application #	DISC2-12654
Title (as written by the applicant)	MitoPunch production of iPSC derivatives as therapeutic candidates for in vivo mitochondrial transfer
Research Objective (as written by the applicant)	Cells have mitochondria that contain genes (mtDNA) inherited only from a mother. Mutations in mtDNA causes disease without treatment. We aim to make a cell therapy that treats mtDNA-caused diseases.
Impact (as written by the applicant)	mtDNA diseases can be devastating. There are no therapies, so disease improvement for afflicted individuals using our novel cell therapy would overcome a treatment bottleneck and have huge impact.
Major Proposed Activities (as written by the applicant)	• We will make diseased cells, called fibroblasts, into recipients for new mitochondria containing healthy mtDNA by an FDA-approved chemical treatment that removes the damaged mtDNA. • We will use our invention, MitoPunch, to transfer new mitochondria containing healthy mtDNA into recipient fibroblasts, generating cells called SIMR-fibroblasts, and will validate their creation. • We will convert SIMR-fibroblasts into early stem cells called SIMR-iPSCs to reprogram the functioning of these hybrid stem cells that contain reparative mtDNA, and will validates their creation. • We will make our cell therapeutic, called SIMR-MSCs, by conversion from SIMR-iPSCs, and will validate their creation. In >900 clinical trials, MSCs have been safe for intravenous delivery into people. • We will generate SIMR-MSCs with a biomarker on their mitochondria so that we can track and quantify mitochondrial transfer into target cells and resulting improvements in target cell performance. • Before use in a clinical trial, SIMR-MSCs will be tested for their known ability to transfer mitochondria (now with good mtDNA) into diseased cells, and we will assess for improved cell performance.
Statement of Benefit to California (as written by the applicant)	Our proposal benefits California by providing a candidate therapy for diseases caused by mutations in mtDNA, for which there are no therapies or palliatives. Care for afflicted individuals can be lifelong and costly for families, insurers, and the state. Our proposal supports the taxpayers' commitment to improvements in medical care and provides data for California's academic institutions and healthcare companies, whose success propels hiring and increased economic prosperity for the state.
Funds Requested	$1,384,586
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	75
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. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 6	• The ability to replace dysfunctional mitochondria in patients has the potential to provide regenerative therapies to those suffering from mitochondrial diseases. • MitoPunch, the mitochondrial delivery technology, has high potential as a tool to engineer the mitochondrial genome and correct mitochondrial dysfunction. • The proposal focuses on mitochondria, and the impact of the mitochondrial genome and variation as a disease risk. Replacement therapy with wild type mitochondria as part of a cell therapy approach has potentially broad clinical applications. • The proposal presents a plan for early stage discovery involving generating the SIRM-MSCs and evaluation of mitochondrial transfer to iPSC-derived and reprogrammed cardiomyocytes in vitro. These are useful proofs-of-concept. • Mitochondrial replacement represents one bottleneck in cell therapies to treat mitochondrial diseases. Using these cells in vivo to transfer mitochondria faces significant additional bottlenecks in delivery, safety, and longevity of treatment. • The ability to remove dysfunctional mitochondria and replace these with functional mitochondria would accelerate generation of autologous cells that have potential as cell-based therapies. • Yes, though this proposed mitochondrial transfer therapeutic approach is only at a very preliminary stage at present. If the basics of this method pan out and are sufficiently efficient, this approach might allow the production of therapeutic, immunologically-matched cells containing replaced mitochondria for treatment of human mitochondrial disease. • This method might allow the production of patient-matched cells. This would be a unique resource. • The existing application is entirely in vitro. The ultimate success of this approach for therapeutic purposes will hinge on whether this approach can correct mitochondrial disease in vivo. • Though the applicants have a good vision for eventual translational research and therapeutic development, the very preliminary state of this work and lack of proof of concept data to show that mitochondria-corrected cells can have a therapeutic effect in vivo renders considerations of ultimate therapeutic applications premature. • As a cell-based therapy, development of the SIMR-MSCs is very early stage. There are significant hurdles to in vivo use of these cells. • Progression from the end of this study to translation is vague. In vivo evaluation is not discussed. Specific disease indications are not considered in the translation plan.
No: 2	*none*
GWG Votes	**Is the rationale sound?**
Yes: 5	• The rationale for making mitochondrially corrected cells is sound, being based on the ability of this group to produce fibroblasts, introduce mitochondria with a novel device, and produce stable isolated mitochondrial recipient (SIMR) cells.

	• The applicants propose to use mitochondria depleted fibroblasts, transfer mitochondria, transform the cells into iPSCs which can then be differentiated in a variety of other cell types. While logical and well supported, the process appears complex and some of the bottlenecks have not been discussed in sufficient detail. • A key question for the proposed application is whether enough mitochondria can get transferred to donor cells. There is limited preliminary data and additional evidence would substantially strengthen the proposal. • There are significant concerns about the scientific basis for a therapeutic use of these cells. It may be very difficult to introduce enough corrected cells to achieve a therapeutic effect, and this depends on which organs are affected by mitochondrial disease. • Though a very few reports show that mitochondria can be move from cell to cell, it is unclear if this phenomenon is sufficiently efficient to yield a therapeutic outcome. In addition, transfer in vivo will only add (but not replace) corrected mitochondria. • Most mitochondrial diseases are multi-organ in nature.
No: 3	• The premise here is innovative and creative. The idea that mitochondria can be replaced in therapeutic cells is promising and has the potential to treat a variety of mitochondrial disorders. • The team provides preliminary data establishing the use of MitoPunch for long-term stable mitochondria replacement in fibroblasts. • The team provides their reasoning for exploring an autologous rather than an allogeneic strategy of mitochondrial transfer. Their reasons are potentially correct, but speculative at this stage. Their manufacturing process is very complex and expensive. Demonstration that allogeneic cells are not effective in mitochondrial transfer is warranted before developing autologous strategies. • The proposal neglects known challenges of MSC therapies. While safe, their effectiveness is has been underwhelming because of low survival. • Most mitochondrial disorders affect multiple organ systems. In vivo delivery of the cells and mitochondrial transfer is likely to be exceptionally difficult. • The project reprograms the fibroblasts, then differentiates to reset the metabolomic and epigenetics of the cell. This seems logical, although it isn't directly shown this is necessary for mitochondrial transfer.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 2	*none*
No: 6	• The study is designed to generate cells with dysfunctional mitochondria replaced by functional mitochondria, then to demonstrate the ability to transfer these mitochondria to cardiomyocytes in an in vitro co-culture model. If successful, these results will warrant evaluation in animal models and for specific mitochondrial disease. • There are some good basic cell functional assays proposed including respiration (oxygen use) assays, and contractility of cardiomyocytes to be produced by differentiation of iPSCs. • Aims 1 and 2 are replicating preliminary data in fibroblasts derived from donors with mt DNA mutations. While incremental in nature, this is an important part of model building. • Proof-of-concept of mitochondrial transfer from SIMR-MSCs to CMs in vitro in Aim 3 is well-designed. The use of fluorescent labels to track mitochondrial via imaging is a good approach. • Characterization of the cells after selection and mitochondria replacement is clear and comprehensive. • Effects of mitochondria replacement on cell metabolism and other phenotypes is carefully considered. • Appropriate mitochondrial disease models are chosen and compared to wt fibroblasts. • The specific disease models investigated are not well-linked to cardiac therapy. While each of these diseases has effects on cardiac metabolism and hypertrophic cardiomyopathy is often associated with the disease, the linkage to CM phenotypes in

	vitro is not clear. The experimental plan is not focused on correcting disease phenotypes. ● The experimental plan fails to account for MSC-CM fusion, which would appear to provide mitochondrial transfer but is different than the proposed mechanism for transfer between cells. ● Improvement/optimization of mitochondrial transfer is not described. This is likely to be a significant roadblock toward use of this technology in vivo. ● While useful in ways, the in vitro co-culture model is not a good model for mitochondrial transfer in vivo. An in vivo evaluation is important for moving toward translation. ● At this stage, the lack of consideration of disease and the lack of in vivo delivery would leave the candidate significantly short of translational potential. ● There is no plan to test the mitochondrially corrected cells in vivo, and extensive animal studies using a model for mitochondrial disease would be needed prior to having a candidate therapy ready for translation. ● The plan is also to do whole genome sequencing to see if the recipient cells have been genetically damaged by the treatment necessary to produce fibroblasts. However, there is no existing preliminary data on this, and if damage does occur at even moderate levels, this could kill the approach as a therapeutic strategy down the road. ● There is no alternative plan to address genetic damage if it is produced in the course of cell production. ● The translational aspects of this strategy are too early for primetime.
GWG Votes	**Is the proposal feasible?**
Yes: 6	● Yes. The milestones are clear, logical, and likely to be achieved in the timeline specified. ● Finely grained milestones are provided that are in line with project goals on cell line engineering and evaluation in vitro. ● Yes—the novel mitochondrial transfer device has been developed by this group, and there is good evidence of mitochondrial research expertise by the research team. ● The team has worked together in development of the Mitopunch technology. Clear expertise in metabolism and mitochondrial biology is present. ● The team is highly qualified to conduct the proposed experiments. ● The resources and budget are appropriate. ● Expertise in cell therapy, especially in vivo models and cell delivery, would accelerate development of the therapeutic. ● The success criteria are generally not quantitative in nature.
No: 2	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 8	● The results of this proposal can benefit the population of CA. ● Mitochondrial disease impact the diverse population of California and the strategies developed here have the technical potential to improve treatment of mitochondrial disorders across the population. ● There is a good account of the diversity of LA county, and cells from a diverse set of donors will be used for these studies. ● The project will use fibroblasts from multiple donors but the plan does not directly consider effects of diversity on project outcomes.
No: 0	*none*

Application #	DISC2-12360
Title (as written by the applicant)	Matrix Assisted Cell Transplantation of Promyogenic Fibroadipogenic Progenitor (FAP) Stem Cells
Research Objective (as written by the applicant)	We seek to develop a cell based-hydrogel therapy to improve outcomes in patients with muscle degeneration. The technology will improve muscle through sustained release of cell-based cytokines.
Impact (as written by the applicant)	While designed for rotator cuff injuries based on the model, low back pain and spinal degeneration as well as traumatic muscle loss would be well served by this therapeutic.
Major Proposed Activities (as written by the applicant)	• Evaluation of pro-myogenic activity of human Fibroadipogenic Progenitor-Brown Adipose Tissue (FAP-BAT) in co-culture experiments. We will confirm the ability to isolate human FAPs and differentiate into a pro-myogenic subpopulation of myogenic FAPs. • Optimization of hydrogels for engrafting of BAT-FAPs. We will select one candidate HyA hydrogel formulation that allows for the highest pro-myogenic and beige fat gene expression of implanted FAP-BATs • Characterization of Matrix-associated autologous chondrocyte transplantation of BAT-FAPs in a delayed rotator cuff repair. We will implant hydogels + FAPs in a delayed rotator cuff repair model to determine effects on muscle quality.
Statement of Benefit to California (as written by the applicant)	The proposed research will be of significant impact to the citizens of California. Given the aging population, an increasing number of California citizens are likely to develop rotator cuff injuries and other conditions that result in muscle degeneration. If successful, this product would offer the first treatment to treat localized muscle atrophy and degeneration through a cell based transplant strategy that stimulates exogenous and endogenous delivery of promyogenic factors.
Funds Requested	$1,221,120
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 70

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

Mean	70
Median	70
Standard Deviation	1
Highest	70
Lowest	67
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 5	• The therapeutic is aimed at providing promyogenic activity where there is muscle degeneration, fatty infiltration and a need for surgical repair. Rotator cuff (250K cases a year) is the most obvious clinical target. Spinal fusion surgery (300K procedures a year) may also be a target. • The proposed approach is equivalent to Matrix-Assisted Cell Transplantation (MACT) for cartilage repair. In MACT, cells are implanted into the lesion after seeding into an appropriate delivery scaffold. • The applicants intend to use Fibroadipogenic progenitors (FAPs), that can be isolated from torn rotator cuff with greater yield from the most severely damaged muscle/tendon. FAPs can be readily differentiated to a Brown Adipose Tissue (BAT) phenotype, which acts as a good inducer of satellite cell differentiation. • FAP-derived BAT cells will be combined with a modular hyaluronic acid based hydrogel network for delivery to the lesion site by injection. The hydrogel polymerizes within the injury site, securing the implanted cells in position. • Key features of the hydrogel include peptide chemistry, matrix modulus with biocompatible stiffness, degradation, and sequestration of growth factors.
No: 4	• Patients undergoing surgery for rotator cuff repair (250,000 annually in the United States) and spinal fusion procedures (300,000 annually in the US) could benefit from a Matrix-Assisted Cell Transplantation (MACT) of autologous FAPs differentiated into a beige adipose tissue phenotype (FAP-BAT) that has the capability of inducing satellite cell differentiation and counteract muscle degeneration. • Transplanted FAP-BAT cells could have higher pro-regenerative potential than endogenous FAP in rotator cuff tears. • Innovative modular hyaluronic acid (HyA)-based hydrogels with tunable degradability, mechanical properties, adhesive ligand density and growth factor sequestration potential could promote localization, engraftment and pro-regenerative potential of transplanted FAP-BAT cells. • It is not clear which population of patients with rotator cuff tears could benefit from the procedure. The MACT therapy may synergize and improve outcomes of repair surgery and/or promote regeneration without the need of surgery. The 50-90% current success rate of surgery seems a large range. • The evidence for autologous human FAPs from tears to be able to be differentiated ex vivo into FAP-BAT is lacking especially given that the PI's own studies show that poor patient outcomes are linked to poor pro-regenerative capacity of endogenous FAPs.
GWG Votes	**Is the rationale sound?**
Yes: 6	• PIs have generated enough evidence that FAPs may affect outcomes of rotator cuff regeneration after tear and may represent a target for innovative therapies. • Enough evidence is provided that tear size and donor age affect FAPs isolated from human rotatory cuff tears. • Availability and experience with human FAPs and murine models of disease is a strength. • Co-I has generated data that support the utilization of modular HyA-hydrogels as MACT for optimizing FAP-BAT delivery similar to previously reported cell delivery. • Figure 4 is very intriguing and support the modularity of the hydrogels for optimization of cell delivery. • Hydrogel platform with tunable properties is ideal for optimization studies.

	• This is a complex hydrogel and raises questions about whether such complexity is really needed, whether it functions effectively, and how the construct will be treated from a regulatory perspective given the multiple mechanisms involved. This hydrogel complexity is interesting but poses serious risks for the project in terms of the feasibility of achieving a clinically useful product. Could a simpler matrix format be used? • There is also lack of clarity as to whether the intended therapeutic is intended to be autologous or allogenic. Autologous is implied but this is not specifically stated. If allogeneic, what evidence is there that immune rejection can be avoided? If autologous, presumably the cells will be isolated following surgical intervention. But how long will it take to prepare the therapeutic and what time gap between surgery and injection will be appropriate? • The large majority of data are qualitative (histologic images) and not quantitative and panels are too small to be readable. • Data shown in figures are small and often of poor quality with most statistical analysis lacking. • Histological images shown in support of proposed experiments lack quantifications and not very convincing. • Lots of typos in the text often confuse the reader.
No: 3	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 1	• The plan is broadly logical. Milestone 1 is useful though not a significant advance but will provide good data for future regulatory purposes. Milestone 2 is fine-tuning of the scaffold and will be essential for delivery of the therapeutic although it will not address the key question of how to balance complexity with clinical gain. Milestone 3 is a pivotal mouse model and gait analysis as the primary outcome. There are no major concerns with this plan.
No: 8	• In Milestone 1, details on the quantifications of the proposed assays and on the co-culture methods are largely missing and there are many imprecisions (nanostring does not assess genotype but gene expression profile). It is not clear how the FAP-BAT and stem cells will be separated for phenotype analysis since it's mentioned that will be co-cultured with contact. • In Milestone 2, for co-culture studies transwell will be used while in Milestone 1 the cells will be in contact. The mechanisms of FAP-mediated regeneration is unclear; it is also unclear whether FAP-BAT or stem cell growth factors will need to be sequestered by heparin-containing hydrogels and what the rationale is for separating stem cells from the hydrogel-containing FAP. • In Milestone 3, the proposed lentiviral transduction of FAP-BAT for in vivo monitoring without any feasibility seems unlikely to succeed.
GWG Votes	**Is the proposal feasible?**
Yes: 4	• The work is feasible and can be delivered.
No: 5	• Hydrogel platform was previously developed and likely to be optimized as proposed. • Human FAPs will be available. • Co-culture experiments in aims 1 and 2 will not be performed in a similar fashion. • The project will rely on the capability of FAPs from different donors to differentiate into FAP-BATs. • Therapeutic approach not clear - time gap of cell generation and surgery not addressed. • Great team of clinician scientist with sport medicine expertise and biomaterial scientist with expertise in hydrogel design for stem cell delivery. • Additional personnel will be devoted to the project, including technician, postdoc and graduate students.
GWG Votes	**Does the project serve the needs of underserved communities?**

Yes: 8	• This is discussed. Given the limited number of human donors it will be very difficult to ensure equal representation. • Yes, tear repair affects the diverse population.
No: 0	*none*

Application #	DISC2-12564
Title (as written by the applicant)	Excitatory spinal interneurons from human pluripotent stem cells to treat spinal cord injury
Research Objective (as written by the applicant)	The primary objective of this proposal is to determine the efficacy of excitatory human V2a spinal interneurons differentiated from PSCs to treat spinal cord injury by restoring motor function.
Impact (as written by the applicant)	Currently no therapies exist that are capable of repairing the injured spinal cord. Our therapeutic cell candidate, excitatory spinal interneurons, could address this significant unmet medical need.
Major Proposed Activities (as written by the applicant)	• Activity 1: Optimize differentiation of specific spinal neuron populations - V2a - from human iPS cells using a fluorescent reporter. • Activity 2: Determine a GMP-compliant iPS cell line that yields optimal V2a donor populations. • Activity 3: Define the optimal dose of transplanted V2a neurons that can be safely administered and integrate with injured host spinal cord. • Activity 4: Determine the minimal amount of time necessary for transplanted V2a neurons to functionally connect and contribute to motor recovery. • Activity 5: Determine the therapeutic efficacy of transplanted V2a neurons derived from GMP-compliant iPSCs to form functional motor circuits following spinal cord injury.
Statement of Benefit to California (as written by the applicant)	Spinal cord injury (SCI) is a permanently debilitating condition resulting from traumatic injury that renders individuals partially or fully paralyzed. The associated life-time health care costs are exorbitant (millions $) and the ongoing need for assisted care impacts family members and friends. A reparative cell therapy for SCI that could restore motor function would benefit the autonomy of the individual and enable a fuller return to society, thereby improving their quality of life.
Funds Requested	$1,512,993
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	0
Highest	70
Lowest	70
Count	12
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	12

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 4	• There are serious questions as to whether this would be clinically feasible to move forward. If someone has come off a ventilator, how could you risk making them worse?
No: 4	• The essential issue is whether this project should go forward at this time. Achieving the neuron phenotype is only a small piece of clinical success in a very complex problem that is treatable, albeit imperfectly. • Fraction of patient cohort who requires a ventilator is very small, therapy would thus potentially only address a small sub population. • It should be clarified who might be a candidate, as those who are chronically ventilated and are not candidates for diaphragm pacing. • Target population for therapy is small and immunosuppression may not be ideal for these patients; the team could benefit from inclusion of pulmonologist with specific expertise. • For meaningful therapeutic effect the success of therapy should be high. • Transplantation in the acute time frame is not realistic especially in initial clinical trials.
GWG Votes	**Is the rationale sound?**
Yes: 5	• Proof of concept is ok but needs to be better grounded in the application. • It's not very clear how brainstem breathing circuits interact with the transplanted excitatory interneurons. • Cells differentiate into glia after transplantation although the focus is to transplant interneurons- this raises the question of where the glial cells come from and how can the cell population be optimized to get to a pure population? Not well addressed.
No: 3	• This is not clear, as so much critical information is missing.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 3	• It's important to define the other cell populations that will be present in the cellular product. • Off-target adverse effects need to be carefully studied as numerous regulatory mechanisms could be affected by such neurons.
No: 5	• The design is largely good except that the transplants they envisage would occur at a later time than in their experiments. • They don't yet have pure interneuron populations, as shown by the fact that the transplanted cells also make glia. Thus, they have precursors, which means that they don' t know whether transplants of pure interneurons will integrate usefully. • They use nude rats while patients will have to be immunosuppressed. • Work in animals poorly explained (ex. nude rats as recipients only explained in budget). • The team needs a pulmonary expert.
GWG Votes	**Is the proposal feasible?**
Yes: 3	• The experiments are feasible, translation will be much more difficult.
No: 5	• It seems unlikely due to the major challenges in transplanting into patients with respiratory challenges. • Timeline not well-rationalized, and is not likely to be done in 2 years.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 7	• Only in the sense that SCI affects individuals across the needs spectrum. • Not sure.
No: 1	• It is important to define how such a complex therapy would actually reach persons with SCI requiring ventilation in underserved communities.

Application #	DISC2-12593
Title (as written by the applicant)	AAV-CRISPR Gene Therapy to Silence the Huntingtin Gene in Huntington's disease
Research Objective (as written by the applicant)	An AAV-CRISPR/dxCas9 gene therapy fused to repressive domains to silence the expression of Huntingtin in neurons as a novel therapeutic for Juvenile and Adult onset Huntington's disease
Impact (as written by the applicant)	Adult or Juvenile patients diagnosed with an expanded CAG repeat in exon1 of the Huntingtin gene. The target patent population would be those early in the disease progression.
Major Proposed Activities (as written by the applicant)	• Validation of plasmids and viral constructs in mouse and human cell models of Huntington's disease • Molecular assessment in human HD cell model following AAV-dxCas9 gene silencing • Production and Validation of AAV-dxCas9 Gene Therapy in YAC mice short term following AAV-dxCas9 gene silencing • Functional Assessment in YAC128 Transgenic mouse following AAV-dxCas9 gene silencing • Molecular and histological assessment in 12-month-old treated YAC128 following AAV-dxCas9 gene silencing
Statement of Benefit to California (as written by the applicant)	It is estimated that one in 10,000 CA residents have Huntington's disease (HD). Health care costs are extremely high for HD patients due to the long progression of the disease, often for two decades. The lost ability of HD patients to remain in the CA workforce, to support their families, and to pay taxes causes additional financial strain on the state's economy. We are designing trials to treat HD through rescuing neurons in the earlier phases of the disease, before lives are devastated.
Funds Requested	$1,379,619
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	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. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 11	• Targeting of the disease causing mutation in genetic disorders is both intuitive and sound in terms of scientific rationale. • Large unmet need despite many clinical trials. Theoretically this disease is a good candidate for gene therapy. Given the devastating outcome of the phase 3 antisense oligonucleotide (ASO) trial, new approaches are needed. • Could be a new approach for Huntington's Disease patients. • It is worth trying new approaches for the reduction of mutant huntingtin (mHTT), even if previous trials using other techniques have failed. • One potential concern with this grant is the possibility that the targeted 30% lowering of the huntingtin gene will not be sufficient. This is supported by the recent failure of the antisense oligonucleotide trial in Huntington's Disease (HD) due to a worsening of the condition of the patients receiving sustained treatment. This worsening occurred despite a significant reduction of mHTT. While I assume this information was not available at the time of submission, it raises serious concerns about the proposed approach. • The expected outcomes of targeted reduction of huntingtin in patient-derived iPSC neurons and in a transgenic mouse model have been met by other approaches but did not work in patients. No endpoints have been added that would predict why this approach should work better.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 7	• Gene silencing using CRISPR in Huntington's Disease might provide an urgently needed alternative approach to ASO which largely failed. • A one-time treatment would perhaps be more affordable than ASO and would avoid the burden of painful repeated injections. • ASO do not target DNA and are thus "leaky" allowing some protein still to be generated, thus the approach presented here seems valid.
No: 4	• The paucity of details relating to the exact method of selecting one allele over the other raises questions about the feasibility of mHTT-specific targeting. Additionally, little explanation is provided in relation to the selection of 30% of the cut-off. • Mutant allele-specific editing should be presented in preliminary data. • Even prior to the failure of the recent trial in HD, published data from the trial demonstrated that reduction of mHTT did not result in a clear change in behavioral/clinical measures. This initial data was from a phase 1 trial, however it is still salient to the application. Therefore, the premise and the read-outs chosen by the applicants are flawed from the start. Additionally, there are a number of problems with the experiments proposed, enough so that the results would not be meaningful in a clinical context. ◦ The proposal is based on the use of the YAC128 mouse of HD, a transgenic mouse model expressing full-length human HTT under the control of the human promoter, which the applicants claim is one of the preferred/most utilized mouse models of the disease. While historically this may have been true, it is no longer the case. The zQ mice series, for example, is much more used and well characterized and addresses several of the pitfalls that were present in earlier transgenic and knock-in models. Additionally, the YAC128 has very little pathology related to mHTT.

	• While the applicants mention early on in the grant that their method will serve juvenile forms of HD, there is no experimental work proposed to address this form of the disease specifically.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 2	*none*
No: 9	• The preliminary data demonstrates that the applicants have the required skills to produce guide-RNA constructs, complete in vitro experiments and perform animal studies. • The preliminary data, as a whole, is very weak. • Guide RNA screening in human HEK293 cells revealed gRNAs that showed 25% decrease of HTT expression. Successfully transfected both cell lines but no outcome data are shown. • Apparently Fig 5 shows downregulation of HHT in transduced neurons in vivo in an animal model? No explanation of figures in the text, the applicant only provides a figure legend. • The weakness in the preliminary data is the lack of a candidate meeting their 30% cut-off for successful completion of the first aim. The lack of even one candidate to transition from milestone 1 to milestone 2 raises questions regarding the feasibility of completing the project within the allotted time frame. • The choice of the model needs to be better justified. • All of the experiments proposed are too superficial. For example, the use of one model is not sufficient. The HD community has long agreed that 3 distinct models are needed to be confident that the results could translate to meaningful clinical benefits. • The behavioral tests are restricted to 2 measures, which is not sufficient to draw firm conclusions of improvements or the nuance between cognitive and motor impairments, which are both critical features of the disease. • The number of animals per treatment group/analyses is not acceptable. This study is significantly underpowered. • Underpowered and no preliminary data on iPSC cells in vitro. • Applicants have failed to meet milestones on previous CIRM funded proposals. • Limited publications resulting from previous CIRM funded proposals.
GWG Votes	**Is the proposal feasible?**
Yes: 8	• Analysis of off target effects seems to be limited to neurons, neuronal phenotype analysis is limited to BDNF withdrawal. • Many details are missing and figures are not explained in the text and aims are somewhat depended on each other - it is not well described how missing milestones inform the work. • Previous CIRM funding on HTT yielded limited results and productivity was on the low end. • There are concerns about the productivity of the team on prior CIRM grants.
No: 3	• The 8-month duration of the animal experiments, while important for evaluating safety and efficacy, requires that within 6 months the lab has generated a guide-RNA capable of reducing mHTT by 30%. According to the preliminary data, no such candidate currently exists, making the timeline rather tight. Further information on how mHTT-specific targeting is occurring would assist in the evaluation of the feasibility of finding such a target quickly.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 11	• Approach would be available to all communities. • Given the samples and resources available to the applicant, it is possible that a product capable of serving a diverse California population will be produced. • The applicants indicate that the clinic with which they collaborate has access to tissue samples from multiple ethnic and racial groups. This should have important ramifications for the project as allele specific targeting frequently relies on SNP expression which can

	be variable between different groups. By incorporating tissue from multiple ethnicities and races, the applicants can help to ensure the applicability of the results to the broadest possible range of patients. • Gender and sex are discussed in less detail, however both male and female mice will be included in the behavioral studies to help address this. Unfortunately, the low number of mice planned for these studies will make evaluation of sex effects rather challenging since only 7 male and 7 female mice will be included in each group for behavior. This number drops substantial for molecular biology experiments where an n of 2 will be included for each sex.
No: 0	*none*

Application #	DISC2-12626
Title (as written by the applicant)	Narrowing the Outcomes Gap: STING-activating iPS-NK cells for the Systemic Treatment of Gynecological Cancers
Research Objective (as written by the applicant)	Induced pluripotent stem cell-derived STING-activating natural killer cells for treatment of lethal and incurable gynecological cancers.
Impact (as written by the applicant)	Limited availability and efficacy of cellular therapeutics for treatment of cervical and uterine cancers.
Major Proposed Activities (as written by the applicant)	• To evaluate the therapeutic efficacy of STING-activating iPS-NK cells for the treatment of cervical and uterine tumors. • To determine the synergistic therapeutic effect of combining STING-activating iPS-NK cell therapy and NK checkpoint blockade.
Statement of Benefit to California (as written by the applicant)	These studies will generate key evidence supporting STING-activating iPS-derived NK cells as a breakthrough therapeutic paradigm for the treatment of lethal and incurable uterine and cervical tumors. We expect the iPS-NK cells developed for this proposal to be widely distributed to the scientific community to advance translational, bench-to-bedside studies, leading to clinical trials, and resulting in direct patient benefit.
Funds Requested	$834,000
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 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	2
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. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 10	• The proposal has the potential for impact through the development of a highly novel stem cell reagent to activate the STING pathway and anti-tumor immunity. • While the proposal is focused on uterine and cervical cancer, the use of an innovative chimeric receptor has broad potential impact in cancer. • The product is an immunotherapy for advanced cancer. Advanced cases are usually difficult to treat and the product represents a novel approach. • Cell product to activate the STING pathway for anti-tumor immunity is a strength. • Engineered receptor is a strength. • Innovation is a strength. • The potential impact will be dependent upon the ability to generate engineered NK cells at scale. This is a major issue that is not fully addressed in the proposal
No: 2	*none*
GWG Votes	**Is the rationale sound?**
Yes: 10	• The rationale for targeting the STING pathway with an innovative approach is sound. Though there has yet to be a demonstration of clinical activity of STING activation, there is no indication that this is because the pathway is not important or relevant. It may be the approach to pathway activation in patients and this novel approach is worthy of full evaluation.
No: 2	• It is not clear that this approach would be active since STING agonists have been clinically tested without activity.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 4	*none*
No: 8	• There is not adequate attention in the research plan to the difficulties in transducing the iPSC-derived NK cells and producing engineered iPSC-derived NK cells at scale for clinical use. • It is not clear that the expansion and differentiation are feasible. The project is overambitious. • The reliance on a lentiviral transduction approach does not adequately address the likely silencing of lentiviral encoded transgenes. • Transgene silencing needs to be addressed. • Preliminary data needed on NK cell manufacturing. • Use of lentivirus for genetic engineering is a weakness.
GWG Votes	**Is the proposal feasible?**
Yes: 4	• No concerns are noted.
No: 8	• The generation of engineered NK cells for STING activation is feasible. The lentiviral transduction approach and scale preparation of engineered NK cells is not demonstrated to be feasible or likely to be feasible with the current approach. • Poor efficiency of stem cell differentiation and capability to generate NK cells in sufficient numbers may be an issue. • It is not clear that the expansion and differentiation are feasible. • NK biology expertise is lacking. • PI does not have a strong track record of long-term funding.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 11	• The proposal specifically addresses a poor prognosis subtype of uterine/cervical cancers that exhibit a racial/ethnic bias in incidence. • Yes.
No: 1	*none*

Application #	DISC2-12455
Title (as written by the applicant)	Creation of a human iPSC-derived microfluidic blood brain organoid barrier for pharmacological testing
Research Objective (as written by the applicant)	To develop a medical device with human stem cells that can simulate the human blood brain barrier for pharmacological testing and disease modeling
Impact (as written by the applicant)	Current blood brain barrier models have significant deficiencies such as lacking shear stress or the 3D cytoarchitecture of the human brain
Major Proposed Activities (as written by the applicant)	• To introduce microglial cells into the human stem-cell derived brain tissue. Microglia are also part of the blood brain barrier but come from a different cellular origin than brain organoid cells • To insert the human stem-cell derived brain tissue into a chamber that simulates blood flow and have it grow until the entire chamber is sealed. • To have blood vessels grow into the tissue in the device • To perfuse the blood vessels in the device and validate that compounds cross it in a similar fashion as compounds cross the human blood brain barrier
Statement of Benefit to California (as written by the applicant)	The proposed research will create an artificial blood brain barrier with human stem cells as a new medical device. The device will allow to test new pharmacological compounds for their ability to cross the human blood brain barrier. This new medical device will benefit the State of California and its citizens since it may accelerate the screening of new pharmacological agents for their ability to cross the blood brain barrier to treat central nervous system diseases such as Alzheimer's disease.
Funds Requested	$785,390
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	66
Median	70
Standard Deviation	8
Highest	75
Lowest	50
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. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 5	*none*
No: 5	• A higher fidelity screening/testing platform for evaluating drug penetrance of the blood-brain barrier would accelerate development of neurotherapeutics. • Existing in vitro BBB models lack a fully physiologic environment which may hamper their performance. Addition of flow and neurovascular unit components in a microfluidic device may advance the technology. • Early stage model development consists of incorporating microglia into cortical organoids, culturing the organoids in a microfluidic device, vascularization of the organoids in the microfluidic device, and evaluating permeability of the vasculature. This represents a logical progression of initial stages of model development. • This model adds significant complexity compared to existing models. It isn't clear that the performance-complexity tradeoff will improve the utility of the models in various applications. For example, the role of microglia isn't evident and the need for the cortical organoid isn't clearly justified. • A translation plan is not evident for using this model in specific drug screening and evaluation applications. It is a complex model and getting this in the hands of researchers will be difficult. • The product, as designed, will lack impact. • Not a BBB model.
GWG Votes	**Is the rationale sound?**
Yes: 3	• No concerns.
No: 7	• The premise that a vascularized organoid can be used to model the BBB is generally sound. BBB function requires interactions between the endothelium and other components of the NVU found in the cortical organoid. In addition, incorporation of shear stress is likely to improve BBB performance. • Preliminary data establish the ability to vascularize gels in microfluidic channels using iPSC-derived cells. • The notion that addition of the proposed cells to a cortical organoid will establish a BBB contradicts an extensive set of literature that shows that BBB properties are conferred early in development by components of the developing brain environment. Differentiated cells added to an organoid are unlikely to acquire BBB phenotypes. • Data do not demonstrate organoid vascularization which is likely to be more difficult than gel vascularization.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 1	*none*
No: 9	• The project provides a logical plan to couple the microfluidic vascularization technology with human cortical organoids. • Methods to induce vascularization by incorporation of NVU cell types and pressure gradients are logical. Evaluation of perfusion of the networks via imaging is strong. • The team has identified appropriate markers to evaluate network formation.

	• Use of fluorescent dextran will permit evaluation of paracellular permeability of large molecules. Small molecules of known BBB permeability will be used to evaluate the model. • The project adds significant complexity without assessing whether that complexity improves performance (e.g. microglia, shear). The investigators should not assume that complexity leads to a better model. • This is a very early stage model development project and even if all goes according to plan, the candidate will require significantly more work to advance to translation. The project does not demonstrate proof-of-concept for a particular drug screening/evaluation application. Benchmarking to other models and to human BBB would be required. Scaling is not considered. • Translation would be accelerated by having a particular application in mind, for example high throughput screening or lower throughput testing of BBB permeability? • The functionality at the end of the day is a concern. • BBB phenotypes are not sufficiently considered. Efflux pump activity and vesicular trafficking, key mediators of BBB function, are not assessed. • The role of the cortical organoid in the model is not clear. Comparisons do not establish the effect of the organoid on the vasculature and vice-versa. • Progenitors need to be used rather than fully differentiated cells.
GWG Votes	**Is the proposal feasible?**
Yes: 4	• The project is organized in a logical manner. Milestones are provided with success metrics. Milestones are linear in nature, but that is appropriate for a short-term technology development project. • The team lacks sufficient BBB expertise. Better understanding of BBB development and physiology would help the team achieve a functional model and guide to high impact applications.
No: 6	• BBB expertise is missing.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 10	• The iPSC line used in this study was derived from cells from a white male. The plan indicates that key results will be validated using iPSC lines from donors from different racial and sex groups. • The applicants note that the literature has not yet established a role of race in BBB function and the role of sex is still undetermined. Development of models such as this may address this question. • The tool would presumably allow predication of drug permeability to the human BBB across a diverse population using iPSCs representative of different communities. It would take significant technology development to get to this point, but this project is a step in that direction. • Streamlining the neurotherapeutic development pipeline may reduce costs of these therapies, making them more accessible.
No: 0	*none*

Application #	DISC2-12583
Title (as written by the applicant)	3D Printed Physiologically Informed Implants for Spinal Cord Injury Repair
Research Objective (as written by the applicant)	Bioprinted spinal cord implants with GMP-grade progenitor cells for patient-specific spinal cord injury repair
Impact (as written by the applicant)	Spinal cord injury which currently has no clinically approved therapies for axonal regeneration and functional recovery
Major Proposed Activities (as written by the applicant)	• We will develop and optimize a rapid 3D bioprinter for printing patient-specific spinal cord implants. • We will develop a biodegradable and biocompatible composite biomaterial for the spinal cord implants to be fabricated by 3D printing. • We will bioprint physiologically informed spinal cord implants with vascularization passages to assist host vasculature network penetration into the implants. • We will bioprint GMP-grade progenitor cells into our biomimetic spinal cord implants and perform in vitro studies to investigate cell-biomaterial interactions. • We will test the optimal bioprinted spinal cord scaffolds in vivo. Functional and anatomical outcomes will be measured in detail in a long-term in vivo study.
Statement of Benefit to California (as written by the applicant)	This project will benefit the State of California and its citizens in three areas. (1) It will provide a cure for the spinal cord injury patients, which will be a life changer for the patients, their families and caregivers. (2) It will be lead by biotechnology companies/institutes based in California which will provide employment opportunities for the local community. (3) It will advance California's leadership position in bioprinting, stem cell research and regenerative medicine.
Funds Requested	$900,000
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: 65

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

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

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 10	• There are currently no clinically approved therapies that can promote axonal regeneration and facilitate the full recovery of motor and sensory functions after SCI. • Templating methods improve outcomes due to their capability to guide regenerating axons growth but have biocompatibility issues and lack the flexibility and capability to customize implants that can fit perfectly into the lesion site of a specific SCI patient. • For treatment of SCI, providing axonal guidance, vascularization conduits, and biocompatible implants for improving outcomes of NSC transplantation are supported by preclinical evidence. 3D printed biomimetic spinal cord implants can significantly improve axonal regeneration and functional recovery in complete transection SCI models in rats. • 3D-printed scaffolds loaded with neural progenitor cells (NPCs) support axon regeneration and form new 'neural relays' across sites of complete spinal cord injury and significantly improve functional outcomes in vivo in rodents. • Inclusion of vascularization channels to allow scale-up to support larger cellular constructs is a strength. • Proposed device will be customized, include vascularization and axonal guidance channels, biocompatible and include induced pluripotent stem cell (iPSC)-derived progenitor cells. • No cure for SCI, potential "home run" if it works, impressive ability to generate matrices, however, a similar study has been done and did not show efficacy. • The SCI environment is complex and may need additional cues to address NSC survival after transplantation, inflammation and wound healing to allow regeneration that allow meaningful functional improvements • Clinical prospective of applicability of constructs to clinical SCI is missing. • Very limited discussion on translation.
No: 1	• Current experience with somewhat similar guidance channels from clinical trials indicates this is very challenging. A carefully designed human trial completely failed. • Describe the type of individual with SCI that might be a candidate for this approach, and how many persons with SCI would fit the approach.
GWG Votes	**Is the rationale sound?**
Yes: 6	• Previously promising pre clinical test with good recovery, idea is to combine the bioprinted matrix with stem cells and also include vascularization factors intended to provide a bridge that is physiologically informed. However the only info will be morphological in nature. • It is unknown if transplanted neural stem cells extend long distance processes in people. Further, we lack methods to prove if that did occur. • It's not really clear why bioprinting cells onto a guidance channel surface is better than loading cells into a channel together with matrix. • It's unclear how the stability of the combined channel with cells will be determined in a realistic time frame for deployment.
No: 5	• Strengths include the 3D printed spinal cord scaffolds with neural stem cells in the channels and NPCs positively expressing appropriate markers. • Scaffolds support NPC engraftment, axonal regeneration and functional outcomes in SCI compared to NPC or scaffolds alone.

	• Strong data on beneficial effects of 3D printed scaffolds to support NPC survival, guided axonal regeneration and functional outcomes compared to NPC or scaffold alone treatment. • Demonstrated the ability of 3D printed scaffolds loaded with NPCs to support axon regeneration and the formation of new 'neural relays' across lesion sites in a severe SCI rodent model. • 3D printed scaffolds can support consistent survival of NPCs loaded inside and filled the lesion site over 6 months while NPCs without scaffolds exhibited poor viability. • Animals that received scaffolds loaded with NPCs exhibited significantly improved functional recovery and formation of the neural connections compared to animals with empty scaffolds or NPC grafts only. • Due to the rapid continuous bioprinting system, the printing speed is much faster, which is critical for cell survival during printing and industrial scale. • To eliminate the UV damage concerns and maintain optimal cell viability, a visible light source is used for photocrosslinking. • Microscale resolution can be reached. • Several biomaterials with and without cells have been successfully printed. • Details on the biomaterial used and biocompatibility are lacking. • The rationale for including vascularization channels and oligodendrocyte precursor cells is not supported by preliminary data. • The clinical applicability of the SCI model proposed is not discussed. • Despite the promising results, a reactive cell layer at the site of implantation of the scaffold is observed but discussion is lacking. • Scaffold mechanical properties are shown but implantation site control is missing to confirm mechanical properties matching
GWG Votes	**Is the proposal well planned and designed?**
Yes: 4	• The idea that laminin might be needed and neurotrophins might need to be incorporated establishes that this project is at a very early stage and not at all ready to be finalized toward a specific device-biologic for regulatory submission. • It's unclear how the optimal relative proportions of glial and neuronal cells will be evaluated. What are the assays for this? • Interesting preliminary data on behavior, little info on the cells pitfalls revealed real shortage of knowledge. • Goals are not clearly spelled out.
No: 7	• Goal is to improve over already promising results. • Strong preliminary data with scaffolds and NPCs. • 3D printing approach showed promising results but rationale for modifying it is weak. • The plan is not clear enough. • Proposed approach is unclear and lacks important experimental details. • This section is poorly developed lacking important experimental details, proposed work and expected outcomes. • The experimental conditions to be tested are poorly justified. • Very minimal discussion of potential pitfalls and alternative approaches. • Clinical translation is poorly discussed. • The autologous process is not translationally feasible.
GWG Votes	**Is the proposal feasible?**
Yes: 6	• Provide data to support that a human scaled-up implant can have meaningful cell survival after implant. • There is little serious discussion of actual pitfalls.
No: 5	• Collaborators are 1) leaders in iPSC technologies and have established Good Manufacturing Practice (GMP) facilities for producing patient specific iPSCs and their

	derivatives, and 2) well-regarded neurobiologists and neurosurgeons with expertise in SCI. ● The team has access to all the necessary resources to conduct the proposed activities, including the collaborators. ● Adequate budget. ● Timing of using patient derived cells is not addressed, mechanics of the transplantation of the device is not clear. ● Milestones are not detailed.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 11	● Both male and female rats will be included. ● iPSCs from donors with different backgrounds. ● The diversity, equity and inclusion section is too concise and underdeveloped.
No: 0	● This is unclear and was not properly addressed in the proposal.

Application #	DISC2-12634
Title (as written by the applicant)	Development of small molecules to restore function in neurons from Intellectual Disability Syndromes
Research Objective (as written by the applicant)	We use human induced pluripotent stem cell derived neurons from patients suffering from Rett Syndrome. We discover molecules that restore function in Rett neurons by blocking cellular senescence.
Impact (as written by the applicant)	These novel compounds will treat Rett Syndrome, and potentially any other ID Syndrome where neurons suffer from premature senescence
Major Proposed Activities (as written by the applicant)	• Generate small molecules with the ability to block neuronal senescence and enter the brain. We currently have 55 molecules, we will synthesize at least 50 additional analogues based on SAR. • We will perform activity assays in vivo as well as determine which molecules are most likely viable clinical drugs. • We will determine the mechanism of action of our best molecules to understand how they work to restore function in Rett neurons. • We will work with our clinical partner to determine best practices for potential formulation and delivery of molecules, as well as identify appropriate patient populations.
Statement of Benefit to California (as written by the applicant)	The project described here will bring great benefit from families suffering with Rett Syndrome. Our novel small molecules will be translated into drugs that have been shown to ameliorate symptoms of Rett Syndrome in neurons through modeling via human induced pluripotent stem cells. Rett Syndrome strikes 1:10000 live female births, so in a state like California, this means thousands of families are suffering right now, with no treatment options available.
Funds Requested	$1,383,775
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 65

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

Mean	65
Median	65
Standard Deviation	1
Highest	65
Lowest	60
Count	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. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 8	• Restoring neuronal function in Rett disease and other intellectual disability disorders does represent an unmet medical need. • Interesting pre clinical approach with a potential for being useful in many intellectual disability syndromes.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 3	• Rationale to focus on neurons in the in vitro experiments is well supported but no data are shown demonstrating that the compound will specifically affect neurons in vivo too. • Preliminary data in the mouse in vivo model are not shown. • Small molecules have a lower bar for clinical application but the specifics are not addressed. Safety studies and sufficient dosing regimens are not discussed. Also, it is not clear when the dose is considered effective - sole focus on seizures in male Rett animals is used as a clinical outcome. • Senescence in the mouse derived neural stem cells decreased the number of stem cells and progenitors and gave rise to a high percentage of cells that expressed neither stem/progenitor nor differentiation markers. This was not seen with patient derived neurons suggesting differences in the human and mouse model. The discrepancy is not addressed and how it could affect the interpretation of the outlined experiments. • The data in figure 12 are not impressive and state that the compound used was not related to the application?
No: 6	• The in vitro model established is biologically interesting but has unclear relevance to the problem of treating an established disease. • The observations that multiple intellectual disability syndromes show loss of function in epigenetic regulatory proteins is scientifically quite interesting. The possibility that the syndrome is characterized by premature aging is an interesting hypothesis. • Surprisingly, with all of the great interest in senescence and development of compounds to prevent or block there are no comparisons with existing approaches. Thus, it is possible that there are multiple drugs that already have been described that would have the properties in which they propose to invest significant resources. • Another problem is that by the time patients are diagnosed, the nervous system has undergone a great deal of abnormal development. There are no data indicating that, even if the underlying hypothesis is correct, established damage can be reversed.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 2	• Overall reasonable, but studies are only conducted in male mice although Rett syndrome is more prevalent in females. • No safety studies are proposed, the compound is likely to have many cell targets and is not neuron specific. • Seizure is the only outcome measures which is not relevant for the other intellectual disability syndromes that are discussed. • Activity 4 is premature and depends on activity 2 and 3.
No: 7	• Technically, the project is well-designed. Whether there will be a candidate ready to advance to translation seems highly unlikely. • The side effects of the strategy are not well considered.

GWG Votes	Is the proposal feasible?
Yes: 5	• Ambitious but milestones will be reached.
No: 4	• At this stage, two challenges must be met in order for this project to be successful. First, they need compounds and the second is they need to be able to use these compounds to provide proof of concept in the relevant animal model.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 7	• Intellectual disability disorders do not segregate for race, ethnicity or other variables of this nature. • The capacity to treat intellectual disability disorders is of great interest, but there's always the concern that the cost of treatment is going to limit the availability.
No: 2	• Study is only done in males.

Application #	DISC2-12341
Title (as written by the applicant)	Developing Universal Donor Endothelial Cells from Human IPSCs for Revascularization
Research Objective (as written by the applicant)	Universal endothelial cells that are safeguarded with suicide genes will be derived from genetically modified human iPSCs to reconstitute vasculature and restore blood perfusion in ischemic tissues.
Impact (as written by the applicant)	Many patients with vascular disease need treatment other than angioplasty and bypass surgeries. Transplantation of universal endothelial cells can alleviate these vascular diseases in a timely manner.
Major Proposed Activities (as written by the applicant)	• Genetically edit a male and a female human iPSC line using CRISPR/Cas9 to generate suicide gene-safeguarded universal iPSCs (su-iPSCs). • Generation of suicide gene-safeguarded universal ECs (suECs) with high purity through elimination of the undifferentiated iPSCs and early germ layer progenitors. • Assess the su-iPSCs and su-ECs for efficient elimination and low immunogenicity both in vitro and in vivo. • Enhance engraftment of su-ECs using peptide-modified collagen hydrogel and evaluate their therapeutic effects in a mouse model of limb ischemia.
Statement of Benefit to California (as written by the applicant)	Cardiovascular diseases are the leading cause of death in the U.S. Despite remarkable advance being made in angioplasties and bypass surgeries for the treatment of vascular diseases, many patients are not suitable for these treatments. Therefore, there is a significant unmet medical need to develop new therapies for these patients. We propose to develop a novel human iPSC-based cell therapy to treat vascular disease, from which patients in California will benefit.
Funds Requested	$1,410,494
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	62
Median	65
Standard Deviation	9
Highest	70
Lowest	50
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 4	• A number of studies have shown that iPSC-derived ECs have therapeutic potential to treat vascular disease. In a murine hind limb ischemia models iPSC-ECs enhanced reperfusion in the ischemic limb. The development of an universal iPS-derived EC for acute use, could be a ground breaking technology, making the proposed technology highly relevant. • Potential "ready-to-go" cell product.
No: 6	• Currently there are only a limited number of treatment options available for patients with vascular occlusive diseases. New treatment methods incl. cell therapy provide an opportunity to improve current treatments. • Preliminary data shows that endothelial cells can be used for the treatment of various vascular diseases. However, theses findings are sometimes discrepant and there is still considerable discussion in the field. • The proposed development of a universal line might accelerate the development a of novel treatment. However, the research in this area is still underdeveloped. For example it is not clear what cell type contributes to the observed effect. • There is no evidence that endothelial cell transplants help with vascular diseases. • Lack of translatability potential.
GWG Votes	**Is the rationale sound?**
Yes: 6	• Appropriate: First, to induce suicide by inserting two inducible suicide gene; Second to make universal cells; Third engraftment in ischemic tissue. • Some preliminary data. • There is limited preliminary data provided. At this time, it is not clear that the proposed cell line is the best cell type for the proposed approach. • Cell type, and the mechanism through which the proposed cells affect the disease under investigation is not clear. Developing a cell line for use in humans is therefore premature.
No: 4	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 3	• The proposal describes in details the proposed experiments for three important milestones: First, to induce cell suicide of Oct4 positive cells for specific removal of the undifferentiated iPSCs; Second: Universal EC by inducing immunosilencing EC cells; Third : Promote engraftment with matrigels. • Not original.
No: 7	• The applicant proposes to make a cell line which can be used in humans. This is clearly premature. • The proposed experiments are well developed and there is sufficient expertise.
GWG Votes	**Is the proposal feasible?**
Yes: 6	• The proposed milestones are achievable and well developed. • The team is qualified. However, there appears a lack of expertise re: the manufacturing of clinical/therapeutic grade cells. The proposal lacks a discussion of these requirements. The proposed cell line is clearly not suitable for use in humans.
No: 4	*none*

GWG Votes	Does the project serve the needs of underserved communities?
Yes: 8	• Yes, it will meet unmet medical needs for people in CA.
No: 2	• There is no discussion of how the proposed research will impact underserved communities.

Application #	DISC2-12374
Title (as written by the applicant)	Treating advanced retinal degeneration diseases using a tissue engineered co-graft
Research Objective (as written by the applicant)	Study will look into the feasibility of using co-grafts made of human embryonic stem cell (hESC) derived retinal organoids and polarized RPE monolayer to treat advanced retinal degeneration diseases.
Impact (as written by the applicant)	A new cell replacement therapy for currently incurable retinal degenerative disease conditions where both photoreceptors and retinal pigment epithelium cells are irreversibly damaged.
Major Proposed Activities (as written by the applicant)	• Preparation of hESC-RPE implants and hESC-RO sheets for making co-grafts. • Construct co-grafts using hESC-RPE and RO sheets. Test different adhesion techniques and choose the most desirable candidates for rat efficacy studies. • Validate successful co-graft implantation technique based on in vivo rat experiments to select the most suitable candidate for conducting the final efficacy studies (Activity 4). • Demonstrate long-term survival and integration of the co-graft (grafts chosen based on Activity 3), assess its morphological integration and visual functional improvements in dystrophic rats. • Validate successful subretinal implantation, survival, integration and functionality of the selected test candidate in a large animal disease model.
Statement of Benefit to California (as written by the applicant)	The proposed study is aimed to develop a cellular therapy for advanced retinal degeneration (RD) diseases by co-grafting retinal pigment epithelium (RPE) together with retina organoid (RO) sheets. Our preclinical experimentation will seamlessly and quickly be transferred into starting clinical trials to develop a novel treatment strategy. Ultimately, hundreds of thousands of Californians with currently incurable RD conditions would benefit from our research.
Funds Requested	$1,290,414
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 60

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

Mean	62
Median	60
Standard Deviation	4
Highest	75
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. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 10	• AMD is the leading cause of vision impairment and blindness among elderly. The majority (85-90%) of AMD cases are dry AMD with no effective treatment at present; estimated that over 450,000 of Californians will suffer from AMD with severe vision impairment by 2020. Even using National Eye Institute numbers from 2003 and adjusting it for the population of California, the costs for California exceed $8 billion • Goal is to translate basic science discoveries related to human pluripotent stem cells (hPSCs) derived retinal pigment epithelium (RPE) and retinal organoids (ROs) into a new treatment strategy for late-stage RD diseases, such as age-related macular degeneration (AMD) and retinitis pigmentosa (RP). • Transplantation of hESC-RPE is not sufficient to restore photoreceptors and transplantation of SC-derived RO driving formation of photoreceptor without a healthy RPE layer and Bruch's membrane is not long-lasting. Thus, co-transplantation of hESC-RPE and RO represents the most promising solution for long-lasting therapeutic treatment. • I like the fact that this is a multi cell model transplant, and think this has a much higher likelihood of success than a single cell type like a RPE iPSC cell line. • Studies will be performed in both rats and large animal models; surgical procedures and implantation instruments have been designed and will be tested. PI is currently involved in clinical trials with hESC-RPE. • This is a resubmission for a project that is a continuation of a previously funded proposal with similar goals. While the progress report of the previous grant is now provided, it is unclear which limitations of the product still needs optimization and how these modifications will increase success. • Discussion on future steps is limited; testing will be made in immunodeficient rats so effects of immunosuppression (which will be necessary in humans) on construct engraftment won't be tested; genetically engineered SC lines are not translatable. • Premature.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 4	• For AMD yes, it is not really a single cell type that is affected given the multifactorial insults and age related epigenetic factors.
No: 7	• Ongoing clinical study supported by positive preclinical studies on transplantation of hESC-RPE. • Rationale for including RO in hESC-RPE transplants is clear and focused on providing photoreceptor regeneration for long-term functional improvement of vision. • Preliminary data clearly show that the assembled team has the necessary expertise to complete the proposed studies. • Advanced methods for assessing functional outcomes are available. • SCs will be used for both RPE and RO generation. • Proposed studies will help understand whether inclusion of the RO will improve functional outcomes (already promising) of RPE transplantation • The main rationale from the proposed studies comes from the previously funded project which focused on fabricating and testing essentially a similar product. It is unclear which

	aspects of the product still need to be optimized based on the previous studies. The limitations of these results justifying the current proposal should be clearly outlined. • Only positive data are shown from the pilot study and statistical comparisons and experimental details are lacking. • Superficial approach.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 1	• I like the aspects that that the PI approached and has now incorporated. ie. histopathology and adverse events.
No: 10	• hESC-RPE fabrication was previously successful and hESC-derived RO previously established. • co-grafts of hESC-RPE and RO will be fabricated either with or without bio adhesives to increase biocompatibility. • Immunodeficient RCS rats will be inbred and used for experiments to exclude the effects of immunosuppression of co-graft engraftment. • Novel recording systems will be used for advanced mapping of the superior colliculus (SC) responses. • New OKN testing method with constant viewing distance for reliable measurement of OKN visual activity. • Large animal experiments with immunosuppression for translatability. • Team, expertise, functional assessments, clinical study with hESC-RPE are strengths. • Not sure how the genetic reporters will help improve outcomes of the co-culture; also, if cells will be sorted based on reporter expression, this step will decrease translation potential. • Studies from previous grants concluded that alginate was the optimal adhesive; however, it is now proposed to test other adhesives and non-adhesive conditions without a clear rationale. • The experimental groups in some of the experiments proposed are not clear; sometimes they are indicated in figures but not cited in the text. • Because in humans, immunosuppression will be used, immunocompetent rats with immunosuppression should also be included. • The model systems need to be refined. • The proposal has a lot of repetitions in the different sections; expected outcomes are poorly described; experimental conditions are not always specified. • Very limited section on potential pitfalls and alternative approaches. • Needs more details.
GWG Votes	**Is the proposal feasible?**
Yes: 5	• The immunotherapy will always be a concern and the risk of adverse events with the immunotherapy.
No: 6	• Clear milestones. • PI is involved in preclinical work that led to a study which is being evaluated in an FDA–approved phase1/2a clinical trial. • A key person developed a procedure to transplant retinal progenitor sheets to the subretinal space in different retinal degeneration models. • A key person developed a variety of genetically engineered reporter stem cell lines designed to label a host of different retinal cell types including rod and cone photoreceptors and will provide the RO. • A key person is biomaterial expert and will provide the thermoresponsive polymers for conducting RPE growth and biomaterials for making co-grafts. • A key person is an ophthalmic surgeon specializing in device and therapeutic development for the treatment of retinal diseases and will lead the in vivo team, mainly the large animal model studies. • Adequate resources.

	• Milestone success criteria do not describe quantitative expected project outcomes and in some instances contain experimental methodologies Timeline is repeated • No.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 11	• There is still a large unmet need for AMD - especially dry and given the multifactorial aspects the disease drug therapy have struggled to show efficacy. A multicellular co graft has a possible approach for success thus improving and supporting a few cellular factors. • Both male and female rats will be included. • Adequate discussion on diversity, equity and inclusion in research for each team member.
No: 0	*none*

Application #	DISC2-12273
Title (as written by the applicant)	Molecular manual for human hematopoietic stem cell development
Research Objective (as written by the applicant)	Molecular map for human blood stem cell development that will be used as a manual to guide pluripotent stem cell differentiation in culture to improve the treatment of blood disorders.
Impact (as written by the applicant)	This will improve the treatment of inherited and acquired blood and immune disorders by ultimately enabling new sources of hematopoietic stem cells for transplantation
Major Proposed Activities (as written by the applicant)	• Perform single cell RNA and ATAC sequencing on human blood forming tissues at different stages of development to establish a molecular manual for human hematopoietic stem cell development • Define the molecular identity of blood forming stem cells during human development and establish scorecards with markers corresponding to each stage of blood stem cell maturation • Identify the vascular precursor cells from where blood stem cells emerge and establish scorecards that mark specific stages of endothelial to hematopoietic transition • Use the molecular manual of blood stem cell development to identify signaling switches that direct blood stem cell specification from endothelium and maturation to functional HSCs • Compare blood stem and progenitor cells generated in culture from pluripotent stem cells to the cells that develop in vivo, and define the developmental stage that they most closely match • Utilize the molecular manual and landmark genes for human blood stem cell development to guide the differentiation of blood stem cells in culture
Statement of Benefit to California (as written by the applicant)	This work will benefit the citizens of California by ultimately enabling the development of new sources of hematopoietic stem cells and other blood and immune cells for therapies. These findings may help overcome the limitation of HLA matched blood stem cells for ethnic minorities and individuals of mixed ethnic backgrounds. These findings will also help generate better culture models for hematological diseases such as sickle cell anemia, and understanding blood diseases that originate in utero.
Funds Requested	$500,000
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 60

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

Mean	61
Median	60
Standard Deviation	17

Highest	85
Lowest	25
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. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 6	• Despite over a decade of intense effort, adult HSCs with full functionality have not been produced, probably because insufficient basic developmental information about lineage and progenitor cell populations leading to HSCs during human embryogenesis is lacking. This grant will yield such useful human HSC developmental biology information, which may ultimately yield the long-sought capability of the reliable production of HSCs from human pluripotent cells (hPSCs) and hiPSCs. • There is indeed a very substantial unmet medical need to produce HSCs in vitro—this could address the treatment of leukemias and other blood disorders, and should they be capable of erythropoiesis, provide a resource of matched red blood cells. • Unique opportunity for CIRM to support this foundational study in the field. • There was consensus on the panel that the generation of large amounts of basic data on gene expression in hematopoietic stem lineages would be of value to science. The field has reached a bit of a standstill, and it is time to go back to basics in a comprehensive unbiased way. So, if the proposal had only been about data generation, and nothing else, the panel may have liked the proposal. However, in that case, it probably would not have been responsive to the program announcement, which requires more than just data generation. • Everything other than data generation in the proposal seems to be vague, lacks utility, or lacks rigor.
No: 3	*none*
GWG Votes	**Is the rationale sound?**
Yes: 4	• The plan is to go back to the drawing board and simply collect single cell transcriptome data from relevant human embryonic cells (HSC progenitors) from early embryonic cells, to cells differentiating in the embryonic liver (liver hematapoeisis) and finally in the bone marrow. • One deficiency of the proposed method is that, despite careful and comprehensive scRNA seq analysis of human progenitor cells leading to HSCs can be performed, there is still no way to definitively perform lineage tracing in human embryonic samples.
No: 5	• The proposal lacks key elements: no hypothesis, no analysis, no meaningful bioinformatics, no statistics, no useful tool.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 1	• The outcome of this work would be a "handbook" with cell-type data gleaned from scRNA seq and ATACseq assessments that could then be used to harness the potential of patient-matched HSCs produced from iPSCs and hiPSCs. • The inability at present to produce HSCs from PSCs by directed differentiation is a substantial bottleneck. This project might lead to the production of HSCs, especially if the biological data from the human embryonic developmental data can be harnessed to produce HSCs.

	• Yes—the progression is rather obvious but sound: 1. Gather needed data on human cellular embryology leading to HSCs, then 2. See if this can be applied in vitro to direct the differentiation of hESCs and hiPSCs to HSCs.
No: 8	• There was a general failure to respond to previous criticism. The previous comment about machine learning was in part a suggestion that rigorous machine learning could be used to create more rigorous deliverables. The only response is "Machine learning is used to complement the scorecard analysis." but this is not actually reflected in the proposal. Where are the related research plan, milestone(s), deliverable(s)? Work by collaborators does not count unless included in the proposal. • Statistics and logistics of generating the single-cell data are not considered well. • Most of the bioinformatics consists of visualizations and/or dimensionality reduction. These algorithms create sometimes pretty pictures but lack rigor and need statistics or other methods for them to become useful. Visualizations are not "maps". The unfortunate acronym 'UMAP' evokes the word 'map' but UMAP creates something more akin to art than a map. There is nothing in the proposed deliverables that is a map. Something like a subway map (e.g., a biochemical pathway) could be considered a map. • Statistics are needed in the proposal. Stating, "The genes for “scorecards” are selected based in rigorous statistical analysis between populations or specific cells." tells us that someone has done statistics in the past. What will be done for this proposal? The fundamental part of Milestone 1 is "additional samples for key tissues/stages are needed to confirm the robustness and reproducibility of the findings, and to gain more statistical power for small populations." This is the only place in the entire proposal words like statistics or power are found. If increasing statistical power is the crux of the milestone and therefore the entire proposal, at least a paragraph if not an entire section on power analysis is needed. How small are the populations? How much power is needed? What N will it take? What are the units of N? etc... • The current web tool is elegant but lacks utility. In particular it does not allow the user to use the data in ways that the data providers do not envision. Maybe to combine with other datasets, to do statistical bootstrapping, to use some novel R package. But there is text in the proposal that implies the data will be downloadable, so I assume that the current tool is primordial and would be developed to allow more user interaction and download the raw data. A user might wish to do the following: How do I write a script to automate analysis on the website? How do I track provenance and reproducibility of results on the website? How do I export results (images) as a vector graphics file, which would be needed for publication? How do I export results as csv or equivalent, which would be needed for further analyses (e.g., in R)? • Very ambitious with no discussion of potential pitfalls. • Proposed effort is less than 10% for all key personnel. It is unclear how contributors will coordinate to share data and optimize the expertise of collaborators.
GWG Votes	**Is the proposal feasible?**
Yes: 5	• This project is not directly enabled by human stem cell research as it is sophisticated but basic embryological collection of descriptive single cell transcriptomic and cellular identity capture, however, if this basic information can be harnessed and adapted to develop an effective way to produce HSCs from PSCs in vitro, the impact would be immense. • The HSC developmental handbook is not in itself a candidate ready for translation. However, if proven and functional HSCs are produced (and despite the good plan, this is not yet in place) then they could easily be adapted quickly for subsequent translational research. • It is feasible because it proposes fairly straightforward dimensionality reductions. But to what end? Perhaps it would be useful to provide some specific use cases and examples where such visualizations have led to value.
No: 4	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**

Yes: 4	• Though this group appreciates and incorporates aspects of research that address ethnicity and race, most of the work proposed is very basic and not yet at a stage where sex and ethnicity should be addressed. However, if successful differentiation to HSCs is achieved, iPS can be performed on anyone's cells from any sex and ethnicity.
No: 5	• This is inherently hard to address with their samples. • The origins of the stem cells to be studied appear to be exclusively European (and/or of unspecified ancestral) origin.

Application #	DISC2-12436
Title (as written by the applicant)	Autologous iPSC-Derived T cell Therapy with Diverse TCRs for Non-Small Cell Lung Cancer
Research Objective (as written by the applicant)	Develop a more effective and safe iPSC-Derived rejuvenated T cell Therapy with diverse TCRs for metastatic non-small lung cancer (NSCLC).
Impact (as written by the applicant)	Our iPSC-derived rejuvenated T cells can target multiple NSCLC antigens with higher tumor cytotoxicity serving as a strong second-line option for patients with resistance to chemo and immunotherapy.
Major Proposed Activities (as written by the applicant)	• T cells are stimulated with organoids of NSCLC tumor cells to enrich the cytotoxic T cells which specifically target the cancer cells . iPSCs are established from the enriched effective T cell pool. • NSCLC-reactive T- iPSCs are differentiated into cytotoxic T cells. The differentiated T cells have the various T cell receptors (TCR) which target NSCLC cancer cells. • Identify the TCR diversity in T cell population derived from NSCLC-reactive T-iPSCs. We identify NSCLC specific TCRs and create iPSC derived T cells that can effectively target NSCLC • Co-culture autologous NSCLC cancer cells and iPSC-derived T cells in vitro to measure the cytotoxic activity. Autologous healthy cells are co-cultured with iPSC-derived T cells for safety assay. • Transplant iPSC-derived T cells into NSCLC organoid-transplanted xenograft models to test the therapeutic efficacy in vivo. We monitor the growth of tumors and survival ratio of mice • Prepare manufacturing plan for first-in-human study. We Participate in INTERACT meeting and address FDA feedback in clinical product development plan.
Statement of Benefit to California (as written by the applicant)	Lung cancer is the leading cause of cancer mortality, responsible for 26% of all cancer deaths. Our iPSC-Derived rejuvenated T cell therapy for metastatic NSCLC will increase patient survival rate. Moreover, there are 28.9 million Americans and 2.8 million Californians lack health insurance that limits access to medical care. Our mass-manufacturing capabilities combined with lower cost makes it possible to offer access to the therapeutic to patients with and without health insurance.
Funds Requested	$867,000
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 60

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

Mean	60
Median	60
Standard Deviation	5
Highest	70
Lowest	51
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. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 6	• No concerns
No: 3	• Unclear. There are several immunotherapies, cell based, for NSCLC. These existing procedures are not compared here, so it is difficult to determine if an already met need is being pursued. Acknowledging this could be an improvement on existing approaches.
GWG Votes	**Is the rationale sound?**
Yes: 3	• Unclear why this T cell subset is the focus. • Lines are personalized, and need to be clinical grade and maintained. Acknowledgement of this, assuming the proposed outcomes are reached, is important. Biological considerations of iPSC from specific patients need to be evaluated. • The challenge is not iPSC reprogramming, the challenge is effective, efficient, and cost efficient differentiation of iPSCs generated. • How will clonal selection and derivation of iPSC be prevented (bulk vs. lines … definition of each is required)? How will T cell clonal differentiation be prevented? This is a major challenge for the field that makes these kinds of approaches difficult. This is independent of Sendai use. • In vitro assessment is required for function prior to in vivo given the cost and labor of in vivo workup. Without this preliminary data, clinical failures using iPSCs technology are likely and should be acknowledged. Eg. the CD8+ may have several defects. • There are no data showing efficiency or ability to generate the T cells. Yield? Frequency? Function post isolation? Functional test prior to in vivo assessment not provided.
No: 6	• The TCR diversity is likely not as diverse as expected and limits the impact of the study.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 0	*none*
No: 9	• The rearrangement or lack thereof of the TCR loci is not well considered. • Scale and manufacturing focused. Operates under the assumption the biology will be defined and workable. • Ignores challenges related to generation of T cells and its function, efficiencies, and cost effectiveness. • Control using clonal or less diverse T-cells should be tested to compare tumor regression based on the hypothesis of the applicant. • Potential pitfalls and alternative approaches need to be better outlined.

GWG Votes	Is the proposal feasible?
Yes: 1	*none*
No: 8	• The difficulties in differentiating iPSCs to functional T cell is not well considered. • TCR specificity after iPSC differentiation may be lost. • The proposal may be feasible as presented but many challenges have been ignored in iPSC maintenance and heterogenous differentiation response of iPSCs from patient and within patient lines. • Expert in differentiation and iPSC biology is required. • Team is in place and budget is suitable for scope of activity.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 9	• No concerns. • Unclear, but not biased.
No: 0	*none*

Application #	DISC2-12637
Title (as written by the applicant)	Stem cell driven regeneration for the treatment of idiopathic pulmonary fibrosis (IPF)
Research Objective (as written by the applicant)	The objective of this work is to optimize a lung localized therapeutic that promotes the reparative proliferative potential of alveolar stem cells.
Impact (as written by the applicant)	The proposed candidate series will promote stem cell-based regenerative repair of the alveolus for treating idiopathic pulmonary fibrosis (IPF), a critically unmet medical need.
Major Proposed Activities (as written by the applicant)	• Optimize suitable lung localized drug candidates using medicinal chemistry. • Demonstrate disease modifying efficacy of drug candidate in rodent models of fibrosis. • Characterize the changes in cellular plasticity in the lung in response to regenerative cues in the alveolus. • Identify a suitable biomarker of stem-cell based regeneration in response to drug treatment for preclinical and clinical use.
Statement of Benefit to California (as written by the applicant)	Idiopathic pulmonary fibrosis affects more than 100,000 Americans and is currently an incurable, terminal disease. Standard of care drugs only slow disease progression and do not address the root cause of the disease. In contrast, our therapeutic promotes alveolar regeneration through a stem cell-based mechanism to target the disease at its core. Funding this proposal will enable the development of safe and effective therapies for the treatment of this devastating disease.
Funds Requested	$1,225,080
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 60

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

Mean	60
Median	60
Standard Deviation	2
Highest	65
Lowest	55
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. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 6	• Yes. New therapies are needed for IPF. • The current candidate drug is already approved, so the pathway to translation is clear. Applicants are also investigating new compounds to broaden their portfolio.
No: 5	• IPF is an age-related disease in which there is accumulation of scar tissue in the lung. There is no consideration of age in any of the proposed models. • It is unclear how much a marker of cell senescence is going to affect the response in this disease. • There are multiple publications of compounds preventing fibrosis in mice. This is a high risk to be another one.
GWG Votes	**Is the rationale sound?**
Yes: 5	• Applicants have successfully screened a fairly large candidate library and identified a lead compound. They are now naturally and thoughtfully following up on this hit.
No: 6	• All the data suggest an anti-inflammatory response not an anti-fibrotic. There are several clinical trials using similar inhibitors in diabetes and cardiovascular diseases. All had to be stopped because of non-positive results.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 2	*none*
No: 9	• There is no consideration of other lung epithelial cells that have stem cell properties, like club cells and basal cells. Recent data suggest a proliferation of these cells to produce pseudo epithelial cells needs to be considered. • It would be important for the team to include an MD or PhD working on chronic lung diseases, who can help in the design and interpretation of the data. • The senescence of the cell needs to be considered better. • "We then screened the comprehensive repurposing library ReFRAME, which contains nearly all Phase 1 drugs" Please provide the number of drugs screened. • No Pitfalls or Alternatives presented despite clear instructions to include them. This is a critical part of any application and was a major factor in my low score. They do mention the development of new compounds (the entirety of Aim 1), which is "sort of" an alternative approach. Perhaps flesh this out and discuss a diverse set of pitfalls. • Define all acronyms first time used (e.g., PCC & KOL). Avoid unnecessary or jargon words and acronyms (e.g. KOL).
GWG Votes	**Is the proposal feasible?**
Yes: 8	• Yes. It is straightforward.
No: 3	• Groups working on AT2 cells in vitro all agree in the difficulty of expanding AT2 cells in vitro. It is unlikely that the data presented support the observation that the drug induces AT2 proliferation in vitro. • The use of lung organoids to study models of infection is appropriate. However, the use of these organoids, composed of epithelial and mesenchymal cells, to evaluate inflammation can be problematic.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 10	• Yes, the drug is generally applicable.
No: 1	• Not discussed.

Application #	DISC2-12301
Title (as written by the applicant)	Characterization and optimization of mutational burden in ex vivo expanded HSC for cell and gene therapies
Research Objective (as written by the applicant)	We aim to develop conditions for safe expansion of blood stem cells outside of the body
Impact (as written by the applicant)	Blood stem cells are a rare but necessary cell type for curative bone marrow transplantation and related gene therapies. Safe expansion of the stem cell will increase therapy availability and success.
Major Proposed Activities (as written by the applicant)	• Characterize and minimize mutational burden in ex vivo expanded mouse HSCs • Characterize and minimize mutational burden in ex vivo expanded human HSCs
Statement of Benefit to California (as written by the applicant)	Blood stem cell availability is a major bottleneck in bone marrow transplantation, a curative treatment for numerous blood diseases. The development of safe culture conditions for blood stem cells would increase blood stem cell availability, and improve accessibility and success rates in clinical bone marrow transplantation. This research will ultimately improve bone marrow transplantation and related gene therapies for patients in California.
Funds Requested	$1,151,183
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 60

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

Mean	59
Median	60
Standard Deviation	5
Highest	70
Lowest	50
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. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 5	• There is a need to ensure that manipulated HSCs are safe.
No: 5	• Improvements in the assessment of mutations in expanded HSC is significant contribution to HSC-based product development.There is no potential clinical impact because this proposal seems not about therapeutic product-candidate development, but is dedicated to method (product testing) development. • There is no clear product at the end of the two years. • No information about existing quality control methods for mutational burden assessment in cell therapy products. No information about existing and competing technologies, where expanded HSC-based investigational products are used for therapies.
GWG Votes	**Is the rationale sound?**
Yes: 2	• The rationale for the assessment of HSC mutations is well presented.
No: 8	• It is not clear why the mouse studies are needed.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 2	• No concerns.
No: 8	• Because the proposal is about the development of the testing method for HSPC-based products, it does not look like it is specifically designed for the CIRM call for DISC2 applications. • It is not clear how it will lead to the development of specific therapeutic product candidate in 2 years. • Mouse-to-mouse experiments are unnecessary. • The mouse studies are not necessary to produce the desired product. • It is not clear why mutation discovery is needed. It seems that it would be sufficient to just screen expanded cells for mutations that arise in clonal hematopoiesis and hematopoietic malignancies since these are the ones that are actually clinically important. • The expansion of human cells is likely to occur in older individuals and the use of umbilical cord blood cells is likely not representative of what may actually happen during expansion of cells from older donors.
GWG Votes	**Is the proposal feasible?**
Yes: 5	• The proposal is feasible (for the development of HSPC products testing methodology). • Based on the expertise of the group and the preliminary data provided the proposal is feasible.
No: 5	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 8	• Yes.
No: 2	• Not addressed in the application.

Application #	DISC2-12710
Title (as written by the applicant)	Product Development of Bioprinted iPSC-derived β cell Spheroid Mesh for Treatment of Insulin-dependent Diabetes Mellitus
Research Objective (as written by the applicant)	Pancreatic beta cell derived from GMP iPSC culture, encapsulated in bioink through 3D photo printing for long-term transplantation into diabetic patients.
Impact (as written by the applicant)	How efficiently mature, functional, and reproducible beta cells to be produced without highly expensive protein factors or less specific chemicals; how encapsulation to be generated with cells inside.
Major Proposed Activities (as written by the applicant)	• Customize the bioprinting process for iPSC-derived β cell spheroid • Evaluate the in vivo immunogenicity of various device designs in multiple implantation sites using empty devices • Evaluate the in vivo GSIS of various device designs in multiple implantation sites using cell device combination products • Characterize the critical quality attributes of the encapsulated product • Investigate the efficacy in the treatment of insulin-dependent diabetes mellitus in mice • Investigate the in vivo safety and biodistribution
Statement of Benefit to California (as written by the applicant)	The application candidate is a California home-grown company with a 21-year history of doing business only in the home State. The outcome of this unique proposal will benefit 20-30% of Californians in their lifetime who will lose some of their pancreatic functions, and likely further damaging their heart and kidney functions, among other things. Furthermore, the other participants are also California-only organizations doing business in this state.
Funds Requested	$1,083,750
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 60

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

Mean	57
Median	60
Standard Deviation	5
Highest	65
Lowest	50
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. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 7	• Bioprinted iPSC-derived β cell spheroid mesh addresses issues of both insulin-secreting cell source and immuno-isolation to allow applicability of beta cell replacement to a larger number of patients with type 1 diabetes. • iPSCs are differentiated using mRNA technology rather than chemical factors, which is claimed to produce more pure beta cells. • 3D printed scaffold deliver the cells while providing immuno-isolation and higher nutrient/insulin transport due to the construct design which is superior to macrodevices. The team has the expertise for optimizing the scaffold design for optimal performance. • Project is early stage and proof of concept with stem cell derived beta cells is not convincing.
No: 4	• New well designed material but issue of packing density is not well addressed, challenge of oxygenation not addressed, issues of insulin secretion not discussed.
GWG Votes	**Is the rationale sound?**
Yes: 4	• Interesting approach.
No: 7	• 3D printing technology capable of manufacturing more stable gels with pancreatic tissue-like properties, tunable mechanical and design properties to maximize stem cell-islet survival, functionality and biocompatibility is a strength. • Preliminary data are limited and figures are poor quality; experimental details are missing preventing complete data understanding; in vivo functional data are not promising; biocompatibility data are missing. • The kinetics of insulin secretion have not been fully considered. • How to provide for the well being of islets has not been adequately addressed (e.g., oxygen supply). • Fig.1 is very low quality with no figure legend; thus experimental details are largely unknown and do not allow data evaluation. • In vivo pilot data shown in Fig.6 lack experimental details; it's unknown which treatment each mouse received; blood glucose normalization is not achieved and dips are only temporary (2 days after transplantation). • In mice, the omentum has a very limited size and is very different than humans. • Fig.7 is very low quality.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 1	*none*
No: 10	• 3D printing technology allows optimization of biomaterial and structural properties. • SC-islets are glucose-responsive in vitro and in vivo studies are proposed to optimize device for biocompatibility and functionality configuration in clinically-applicable sites. • Milestones lack important details and groups to be tested; some milestones are preliminary. • In milestone 1, the islet loading density should take into account scalability; viability throughout the device should be tested by z-stack confocal microscopy; there is no discussion on the conditions that will be tested for device structure as initially mentioned in the rationale section.

	• No viability data is provided. • The choice of implantation site is a concern. • Implantation sites not mentioned and omentum is not applicable in mice; details on examination of immune cell infiltration and fibrosis status of the surrounding tissues are missing. • Not clear how the mouse model will be decided and which devices will be tested. • The viability of cells in vivo is a concern. • Milestone 2 is premature given that the device has not been optimized yet and the project is very early stage. • In milestone 3, since the device should provide also immuno-isolation, testing should be done also in non-immunosuppressed mice unless another scientific question is asked; the dose proposed for human cells in mice is very unlikely to induce diabetes reversal. • Transplanted cell number is a concern. • Use of immunocompromised mice will yield limited translatable results. Overall highly preliminary, poorly described approach. • Neither expected outcomes or potential pitfalls and alternative strategies have been identified.
GWG Votes	**Is the proposal feasible?**
Yes: 5	• Applicants need to demonstrate the ability to make constructs and show that they can change the shape of the constructs. • Limitations are poorly addressed.
No: 6	• Milestones are clear and logical. • The applicants have access to all the necessary resources and adequate budget. • Aim 2 depends on aim 1 and aim 3 on aim 2; given the limited amount of preliminary data feasibility is low. • Very limited expertise in beta cell replacement.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 9	• No concerns were noted.
No: 2	• iPSCs from donors with different backgrounds (i.e., race, ethnicity, sex, and gender diversity) will be used. • For the animal studies, both female and male animals for sex as a biological variable will be used. • Adequate discussion on how the product can address the needs of underserved populations.

Application #	DISC2-12293
Title (as written by the applicant)	Epigenetically stable human Tregs with stem-like properties for graft-vs-host disease
Research Objective (as written by the applicant)	We aim to discover the identity of stem memory Tregs
Impact (as written by the applicant)	We aim to harness the power of stem memory Tregs to improve the efficacy of Treg therapy and preserve the epigenome of Tregs to improve the safety of Treg therapy for graft-versus-host disease
Major Proposed Activities (as written by the applicant)	• Discover and define stem memory Tregs in humans • Characterize stem memory Tregs and develop manufacturing process that preserve them • Test stem memory optimized Tregs in in vivo persistence and protection against graft-versus-host disease in humanized mice • Define molecular events that lead to unraveling of Treg epigenome during inflammatory challenge • Manipulate transcription factors to preserve the Treg epigenome during inflammatory challenge • Test transcription factor stabilized Tregs in vivo stability and protection against graft-versus-host disease in humanized mice
Statement of Benefit to California (as written by the applicant)	Autoimmune, inflammatory and degenerative diseases are significant burdens in modern society. California shoulders a large share of this burden. Treg therapy holds the promise to repair the defective immune system and damaged tissue in these diseases. California has the most active Treg cell therapy program in the world. By advancing Treg therapy, the proposed research benefits California by maintaining the technological lead and providing its citizens early access to novel therapies.
Funds Requested	$1,463,400
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: --

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

Mean	--
Median	--
Standard Deviation	--
Highest	--
Lowest	--
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	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. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 8	• Significant problem with big unmet need. • The ability to impact cellular suppressive immunity is not currently available. • The application of Treg cells to bone marrow transplantation has not been clinically productive.
No: 2	• Despite some attempts to evaluate the therapeutic efficacy and prophylactic effects of Tregs in GVHD, there is no convincing data as of today in favor of this type of intervention. • Other promising therapeutic developments in GVHD should be acknowledged to appreciate the competitive landscape. • It is unclear if the authors will be able to identify and describe smTreg population. This proposal is so far from anything clinical, the clinical significance of therapy by smTreg is unclear. If successful, it will improve Treg-based therapy.
GWG Votes	**Is the rationale sound?**
Yes: 2	• The rationale for the discovery of smTreg population(s) sounds as well as a rationale for therapeutic use of these "enhanced" T-regs for GVHD and other conditions. • The authors present compelling preliminary data to support further development - discovery of smTregs. • The proposal is a "fishing" expedition to characterize a population that has yet been seen in humans. This is a discovery grant and far away from process development.
No: 8	• The rationale for the need for Treg cells in BMT is not clear. • The existence of stem cell like T regs is not clear. • The strategy has been tried before without success, and their approach needs to be differentiated from those studies.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 0	• All proposed experiments are well constructed. • The authors offer too many methods for the discovery of elusive smTregs. The proposal would look better if the authors will focus on fewer but most important experiments. • The authors mistakenly use the terminology "define manufacture process" in aim 1b (figure 8). There is nothing in this proposal defining a manufacturing process. It is a pure discovery and product development project.
No: 10	• It is not clear that the assays can provide evidence of these Tregs. • It is not clear what the epigenetic profiling studies add to the objectives. • Good experiments but not all are well rationalized. • Not a unique approach, has been done before. • This could be a fishing expedition.
GWG Votes	**Is the proposal feasible?**
Yes: 2	• With an overload of methods and experiments, the project looks too ambitious to complete in 24 months. • Some in vivo experiments, like serial transplant to demonstrate stemness of the smT-regs, may take more than a year.
No: 8	• It is overambitious. • No functional assay is proposed.

	• No hashtagging in the single cell sequencing approach leads to inflated costs. • Too ambitious for the funds and timeline.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 10	• Yes. • Yes.
No: 0	*none*

Application #	DISC2-12397
Title (as written by the applicant)	Intracerebral Neural Stem Cell Transplantation to Treat Mucopolysaccharidosis IIIA
Research Objective (as written by the applicant)	To treat Mucopolysaccharidosis IIIA (MPS IIIA) disease, a human neural stem cell line with CNS migratory property will be genetically engineered to produce and deliver the MPS IIIA enzyme, SGSH, globally throughout the CNS.
Impact (as written by the applicant)	Delivering therapeutic proteins to the CNS is a significant bottleneck. The stem cell-mediated protein therapy proposed here may be effective for MPS IIIA and other lysosomal storage diseases.
Major Proposed Activities (as written by the applicant)	• Generate a GMP-compatible stable neural stem cell line by the method previously established by the applicant. • Genetically engineer the cell line with a lentiviral vector, optimized to overexpress and secrete the key therapeutic protein, SGSH, at > 100-fold higher than physiological level. • Create cell banks of the SGSH cell line to generate a research lot equivalent to the planned clinical lot. Characterize the lot for identity, purity, and potency. • Transplant the cells into healthy dog brain using clinically intended device, surgical procedure, and immunosuppressive regimen, to assess clinical feasibility. • Demonstrate reproducible, disease modifying, biological activities by the cell line, in mouse and dog models of MPS IIIA. • Hold a meeting with the FDA for review of data and advice on planned nonclinical and clinical goals.
Statement of Benefit to California (as written by the applicant)	Most of the proposed work will occur in California, with vendors and contractors in California participating in the project. This work will bring a cutting edge stem cell technology to California, adding to the gravity of scientific talents and resources for stem cell research to California. California patients will be some of the first patients to receive the medicinal product in clinical trials as well.
Funds Requested	$1,132,318
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: --

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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. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 6	• MPS IIIA is a rare monogenic disease. The approach developed here would likely advance other efforts for cell-based delivery of proteins to the brain. • Goal is to stop progression in MPS IIIA (MPS3a) an inborn, progressive, fatal neurodegenerative disease. The genetic mutations result in the lack of a lysosomal enzyme, N-sulfoglucosamine sulfohydrolase (SGSH). • A fetal brain-derived immortalized NSC line that overexpresses SGSH has significant potential for treating or curing Sanfilippo syndrome by delivering the enzyme that degrades heparin sulfate. • The candidate has significant potential for improving care of MPS IIIA patients using stem cells to deliver SGSH. The stem cells would presumably differentiate to neural and glial cells in the brain where they would provide long-term delivery of SGSH. • The translational path described is very strong. Activities and milestones are clearly designed toward generating materials and proof-of-concept that motivate translational studies.
No: 3	• Inborn monogenic diseases such as MPS are caused by deficient activity of a single enzyme. There is no FDA-approved treatment for MPS IIIA. • The goal in this proposal is to isolate a stable line of human adherent neural stem cells (hNSCs), with innate migratory property, modified to express high levels of the enzyme defective in MPS IIIA. The hope is that these cells will migrate broadly along white matter tracts, and will differentiate into neurons and glia to "seamlessly" integrate into the CNS.
GWG Votes	**Is the rationale sound?**
Yes: 1	• No concerns.
No: 8	• Use of stem cells to deliver SGSH is a high risk, but sound strategy. Direct delivery of SGSH to the brain has been ineffective, likely due to difficulties crossing the blood brain barrier. AAV-based gene therapy has also met with limited success. The ability of NSCs to generate cell types that will locally secrete SGSH is an idea worth exploring. • Intracerebral infusion that will deliver engineered human NSC using lentiviral correction across major white matter tracts and provide therapeutic benefit is needed. • Whether or not the project is based on sound scientific rationale is up for discussion, as there are multiple ways this project can fail. • Some of the problems that are not addressed are considerations about the migration scale in larger brains. What will happen in the inflammatory environment of the diseased brain where the NSCs will receive signals quite different from those to which they are exposed in the experimental situations discussed? Will the cells drop out of division? Will they differentiate inappropriately? • Delivery throughout the brain and long-term engraftment of a sufficient number of cells to inhibit or reverse SGSH are major challenges compared to other neural cell therapies. • The goal is to have a bank of cells from a single cortical specimen. This means they will need to be applied with the suppression of immune function, and it's not clear how long immunosuppression will be required.
GWG Votes	**Is the proposal well planned and designed?**

Yes: 0	*none*

No:
9
	• The project plan will generate a GMP-compatible NSC line that is conditionally immortalized and lentivirally transduced to express SGSH. The manufacturing workflow is very clearly defined.
	• Animal studies are designed to evaluate biological activity and safety of the cells in appropriate genetic models. If successful the outcomes of a translation-ready candidate will be achieved.
	• The applicant has expertise in cell manufacturing, with experience in cell line immortalization and genetic modifications. The workflow here is clear and detailed. Cell line identity, potency, and sterility testing are generally strong.
	• The applicant will partner with experts in the animal models to conduct animal studies. This is a logical approach. Comprehensive analysis of the animal models is a strength, especially the physiological outcomes. The team will extract as much information as possible out of the limited studies.
	• The project evaluates rather than explores. There is little variation, other than a couple of doses, to optimize performance. Given the expense of the animal models this makes sense, it limits the ability to identify conditions that justify further translational investigations.
	• There is relatively little detail on in vitro studies that will profile safety and efficacy of the engineered cells. There is concern with potential tumorigenicity of immortalized and transduced cells. The in vivo studies will look for this, but more could be done on the in vitro side.
	• There is also concern about silencing of the SGSH expression following NSC differentiation that should be probed prior to in vivo studies.
	• The animal models are complementary but their synergies are difficult to follow. It isn't clear why the healthy large animal study will precede the mouse studies.
	• Large animal studies are underpowered to test effects of dosing.
	• The effects of introducing a cell dose this high (>5B for a human) into the brain are not considered.
	• Distribution of the large amount of cells they propose to use is not shown or discussed.
	• The preliminary data is not compelling and the study is too premature for translation.
	• At present, the demonstrated two-month survival and migration control cells is in nude rats and in an animal model of MPS IIIA that is an immunocompromised animal. They have no data indicating the proposed approach would have any benefit at all.
	• No relevant preliminary data of efficacy in animal models.
	• No discussion of how this approach will be superior to other approaches.
	• There is no data indicating that this approach outperforms the ongoing AAV-based gene therapy trials for this disease, or the ongoing clinical study using genetically modified autologous HSCs.
	• The applicant makes mostly predictions based on very limited preliminary data and no discussion of a plan should some these predictions not occur:
	  ◦ Cells will disperse widely along the major white matter tracts throughout the CNS, acting as a vector.
	  ◦ Cells will differentiate into neurons and glia and seamlessly integrate into the tissue.
	  ◦ Cells will secrete the therapeutic protein throughout the CNS in a continuous and sustained manner, which will be taken up by the host cells and normalize the protein deficiency.
	  ◦ The neural stem cells and their differentiated progenies will also provide regenerative stimulus for some repair of the tissue and some reversal of the patient's neurological deficits.

	● Concept will be applicable to other neuronopathic MPS and lysosomal storage diseases as well as other neurodegenerative diseases such as AD, PD, and ALS. ● No meaningful discussion of pitfalls.
GWG Votes	**Is the proposal feasible?**
Yes: 1	● No concerns.
No: 8	● The milestones are clearly focused on a translational path. Quantitative success metrics are provided. ● The milestone of 5% of wild-type SGSH activity in treated animals demonstrates proof-of-concept but seems low for therapeutic efficacy. ● They generated a number of versions of the construct with the best having a 58% secretion the SGSH. ● Applicants show feasibility of animal surgery. ● There is no testing of critical hypotheses that will be necessarily successful if this approach is to work. ● They comment that their therapeutic dose calculations require just under 6x10(10) cells, which also have to distribute in a uniform manner. There is no evidence that such distribution occurs, and there are no studies on the distribution of cells in the mouse model. ● They say that there are numerous surviving cells, but there is no quantitative information. They say that there is wide migration, but again there is no quantification. ● The also say that there was a 5.5-fold increase in GFP-positive cells over six months, but cells were only injected in the subpial space over the spinal roots, which is not going to be where they would be injected in a treatment. ● Large animal studies are limited to n=1, not sure whether this will be informative. Number of mice used in the safety studies is not explained.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 6	● The applicants state that all communities could potentially benefit from the treatment. ● These rare diseases are not selective for race, ethnicity or other related areas of concern.
No: 3	● Possibly - the cost of these approaches is likely to be high and would not be widely available. ● No sex consideration of host animals.

Application #	DISC2-12535
Title (as written by the applicant)	Development of Stem Cell Therapy for Sanfilippo B
Research Objective (as written by the applicant)	To develop a Stem Cell therapy for Sanfilippo B syndrome
Impact (as written by the applicant)	There is no treatment for Sanfilippo syndrome, and other therapeutic approaches have failed in clinics. This proposal will develop a stem cell based therapy for Sanfilippo syndrome.
Major Proposed Activities (as written by the applicant)	• Generation of universal donor Embryonic Stem Cells (ESC H1) using state of the art genome editing technique • Increase the level of the missing enzyme in universal donor ESC (H1)using state of the art genome editing technique • Differentiate ESC into Brain stem cells in vitro capable of secreting NAGLU (NAGLU-NPC) • Transplantation of NAGLU-NPC to evaluate if the cells can survive in the mouse brain and can repair brain tissue provide NAGLU enzyme. • Transplantation of NAGLU-NPC to evaluate if cells differentiate into functional neuron and integrate in the neuronal networks • Transplantation of NAGLU-NPC to evaluate if cells can repair brain tissue and correct abnormal mouse behavior associated with Sanfilippo syndrome.
Statement of Benefit to California (as written by the applicant)	This application will help develop a stem cell therapy for Sanfilippo B disorder, a pediatric genetic disorder that currently has no treatment. If successful, this approach could be extended to several other lysosomal storage diseases, bringing a therapy for these catastrophic disorders.
Funds Requested	$1,426,350
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: --

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

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

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 6	• Fatal disease with no cure.
No: 4	• The goal of this project is to develop neural precursor cells that secrete high levels of an enzyme (NAGLU) that is defective in the lysosomal storage disorder called Sanfilippo syndrome type B, and also called muccopolysaccharidosis type IIB (MPSIIB). The treatment of this syndrome definitely represents an unmet medical need. • The therapeutic candidate is still at preliminary stages and substantial work is needed before advancing to the clinic. The ESC lines will first need to be genetically edited. Only after successful production and validation of the ESC line can the pre-clinical work be initiated. • Whether this research will result in an actual therapeutic candidate is not clear.
GWG Votes	**Is the rationale sound?**
Yes: 2	• A gene therapy based clinical trial showed reduced storage accumulation but poor reversal of neurological changes suggesting that simply providing the missing enzyme may not correct the disease. The applicant thus proposes a combined cell and new gene therapy. • Positive preclinical observations in mice have not translated to human in many studies. It is thus not clear why the applicant thinks that positive data in the mouse model using the approach proposed would have translational value - a discussion would have been helpful.
No: 8	• Targeting NAGLU enzymatic activity to improve protein degradation and reduce accumulation in lysosomes is a logical target for an enzymatic disorder. However, how the applicant's approach would achieve increased enzymatic activities in surrounding cells is unclear. No explanation of if or how the enzyme would be released from overexpressing cells after transplantation was discussed. • While some preliminary data was provided to indicate beneficial effects were observed, the lack of characterization of enzyme levels leaves the mechanism in question. Additionally, no description of the normal cellular expression pattern of the NAGLU enzyme is provided so it is also unclear whether NPCs are the most appropriate cell type to transplant. • Overall, the preliminary data is very weak. Images of previous differentiation protocols suggest that the successful differentiation rate for neurons is very low (~10%). Such a low differentiation rate could be very problematic in a transplantation study where unexpected cell types could have severe detrimental consequences on the surrounding tissue. • The provided animal data does not show any evidence that the transplanted cells survived and differentiated into neurons or other beneficial cell types. This would be critically important evidence to further proceed with this grant. It is also unclear how the cells were administered into mice for the preliminary data. Based on figure 2, it appears that multiple injection methods were used but it is not clear which method is quantified in the figure. • The idea of correcting an enzymatic efficiency by delivery of the missing enzyme is the basic premise of all gene therapy for all lysosomal storage disorders. These approaches have thus far not been effective. It is important for them to be explored but also to understand why they have failed. • Preliminary data is not compelling.
GWG Votes	**Is the proposal well planned and designed?**

Yes: 0	*none*
No: 10	• Study remains descriptive and correlative. Applicant will not know what was important in the recovery- sustained enzyme or neuronal differentiation or decreased microgliosis. • The data are not particularly compelling. Although engraftment of the cells is possible, and they seem to survive for extended periods, the levels of enzyme achieved in most of the cortical regions examined is actually quite low. • No. The lack of biochemical studies to validate enzyme expression in the implanted cells, as well as in the brain after implantation, put the entire grant on shaky footing. Without a clear demonstration of this basic aspect of the project it is unlikely that clinical translation will be possible. • They suggest that achieving 5% NAGLU efficacy in at least three sections of the brain and nine months will be a positive indication of adequate enzyme distribution. Considering that this disease affects the entire central nervous system, that seems overly optimistic. • There is also no data on enzyme delivery in such areas as the brainstem and spinal cord. • Although the applicant uses language such as "wide distribution of cells," no quantitative data are provided. • Analysis of cells and brain is not sufficient, many experimental details are missing. • Whether a 30% decrease of one of the neural inflammation markers is indicative of adequate rescue also seems overly optimistic. • Applicant states that "Achieving ≥ a significant 30% decrease of one of the neuroinflammation markers in at least half of the brain along the rostrocaudal axis at 9 months post-implantation will be a positive indication of pathology correction"- the rationale for this is not clear as anti-inflammatory agents have not been successful. • They hope that the transplanted cells also make neurons but they have no idea if this is the case. • No data are provided on what happens to the transplanted cells in the diseased mice. This is a very different environment, with many pro-inflammatory signals. Whether the cells will survive, migrate, or differentiate appropriately in such an environment has not been explored. • They only chose to look at a single astrocyte marker, which is insufficient. This is particularly the case because transplantation of precursor cells into an inflammatory environment may lead to the production of reactive astrocytes rather than beneficial astrocytes. • In other places, the markers indicated are not appropriate for the cell population they aim to identify. At one point the applicant states that nestin, a marker of immature neurons, will be used to identify mature neurons, despite the fact that nestin is used in Figure 1 as a marker of neural progenitor cells. These inaccuracies in combination with missing details have generated a plan which is unlikely to advance the procedure to translation. • Diseased environment is not well considered. • Another concern is the age at which the transplant is performed in preliminary studies. They propose to carry out transplantation in one month old animals, but such experiments have not yet been performed. Such experiments are critical, because transplantation will not occur at a clinically relevant developmental stage in an early postnatal mouse or rat. • The focus of the studies on injection into newborn mice is also problematic as this is not representative of the clinical setting. Additionally, all of the studies are underpowered and the descriptions of the methods are confusing and sometimes contradictory. For example, in the description of the injection protocol, the authors indicate that 9 injections will be performed, but the total number of cells they say they will inject corresponds to only 4 injections.
GWG Votes	**Is the proposal feasible?**
Yes: 3	• Some of the experiments can be achieved.

No: 7	• There are many holes in the basic rationale that raise serious concerns about the quality of the project. The lack of clear data that the injected cells differentiate into the appropriate subtypes, in combination with admissions of low survival, make any further plans questionable. Additionally, most of the proposed application relies upon the completion of tasks for which the team has little or no experience. • The overall lack of feasibility takes away from the overall impression of the project. • Only a very superficial description of potential pitfalls is provided. • The applicant raises salient concerns in aim 1 regarding potential low survival of the grafts as well as potential concerns associated with generating an entirely new mouse model. Where this section is lacking is in descriptions of how these concerns will be addressed if they do arise. This is particularly problematic for the animal as the assertion that immunodeficient mice will have the same neuropathology reported in Sanfilippo B mice is based on very naive thinking on the part of the applicants. • The applicant addresses the possibility of differentiation of the implanted stem cells into astrocytes instead of neurons. This is an important pitfall to address given the very low rate of differentiation into neurons observed in the preliminary data. However, it is somewhat odd that no mention of further optimization of the differentiation protocol was made in response to this eventuality. The apparent lack of concern over the possibility of differentiating into unexpected cell types raises questions about the rationale for differentiating into neurons at all. The lack of detailed biochemical studies describing expression of the NAGLU enzyme in different cell types makes it difficult to evaluate how different cell types may impact the expected phenotype. • The aim 2 pitfall section does not provide any mention of potential technical problems. The complexity of the proposed experiments makes technical problems likely, particularly given the lack of experience of the group with such techniques. A description of alternative approaches if the applicant was unable to complete the proposal was lacking. • Aim 3: The applicant discusses the fact that the animal model has physical disease that may impair behavioral testing. This can present a major obstacle to generating reliable data. While selecting an age before physical impairments are too severe for testing is reasonable, motor controls would be required to ensure that these are not interfering with phenotypes. • Additionally, all of the selected cognitive testing paradigms come with significant environmental stressors. While the applicants say Barnes maze can be used to avoid stress, it is unclear how a test that involves bright lights and loud sounds could be considered to be less stressful. The description of the Morris water maze in the pitfalls sections is confusing as this test was not described in the main project proposal. • The timeline seems completely unreasonable given that the applicants do not yet have either the iPSC model, which all of their experiments depend on, or the crossing complete for the animal model. Generally, 6 months to a year are required, at a minimum, to achieve either of these two objectives. • For the iPSC model development, the complexity of the proposed task in combination with the apparent lack of experience with gene editing technology makes it highly doubtful that the task can be completed within a year, never mind the 4 months proposed in the milestones of the grant.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 7	• This is such a rare disease that this really is not a concern.
No: 3	• Assuming that the applicants develop a therapy that could be brought to the clinic, all groups of society could benefit from the therapy from a theoretical standpoint but perhaps not from a financial perspective. • The authors have deployed very little effort, if any, to address these issues either within their project proposal or in terms of recruitment within their group/institution. The justification for this is 2 sentences long and simply reflects a complete lack of consideration. • No discussion provided.

Application #	DISC2-12422
Title (as written by the applicant)	Targeted correction of autologous iPSC-derived RPE with high-risk AMD variants and evaluation of vision rescue in RPE defective murine models
Research Objective (as written by the applicant)	Engineering retinal stem cells by correcting a common genetic risk factor and testing these cells in retinal degenerative rats to assess its potential to treat age-related macular degeneration.
Impact (as written by the applicant)	If successful, somatic cells from AMD patients can be reprogrammed to pluripotency, engineered to correct genetic errors, differentiated to RPE, and transplanted back to the patient to rescue vision.
Major Proposed Activities (as written by the applicant)	• Identify stem cell lines bearing genetic risk factors to develop AMD from our existing stock. • Use CRISPR gene editing technology in stem cells to replace genetic sequences highly associated with AMD with sequences known to protect individuals from developing AMD. • Differentiate CRISPR-engineered stem cells to retinal pigment epithelium (RPE) cells, which are critical in AMD progression. Confirm these RPE have the structure and function expected of healthy RPE. • Expose differentiated RPE cell lines to oxidative stress and compare the structure and behavior of these cells using microscopy, cellular assays, and transcriptome profiling. • Generate retinal organoids from our CRISPR-engineered stem cells that exhibit optimal anti-inflammatory and antioxidant responses. Identify, validate, and isolate RPE sheets for transplantation. • Transplant these RPE sheets into Royal College of Surgeons (RCS) rat models of retinal degeneration and test their ability to restore visual function.
Statement of Benefit to California (as written by the applicant)	Nearly 1 million Californians suffer from vision-related disorders, a significant subset of which are maculopathies caused by degeneration of the retinal pigment epithelium. Unfortunately, most of these conditions have few or ineffective treatment options. The development of new and effective therapies that support the recovery of the damaged retina would not only restore vision in patients with retinal degeneration but also reduce long-term healthcare costs for all Californians.
Funds Requested	$900,000
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: --

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

Mean	--
Median	--
Standard Deviation	--
Highest	--

Lowest	--
Count	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. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 5	• The proposal takes a novel approach to enhancing cell therapy for AMD. Autologous RPE cells will be derived from iPSCs. They will be genotyped to determine which locus is most important for degeneration, using a disease in a dish model. Then correction of the genotype by gene editing will be used to generate cells for testing in a rodent model. The approach is interesting and potentially achievable, but challenging. • Addressing high risk gene but role in pathology is not clear.
No: 5	• The proposed technology will not result in a candidate that could impact any unmet medical need. Techniques proposed are out-dated and not well thoroughly planned. • The fact that they are only looking at a single risk allele, a single cell line does not make sense for an age related multifactorial disease. • There is no detail around the placement location and or the surgical technique. Will the cells be placed in a monolayer and anywhere near the "center" of the vision in order to see an effect? • The rat is not the ideal model and electroretinogram are not sensitive enough to detect a small local change. There is no mention of determining cell polarity and how to risk mitigate that. • The application is not thoughtful. The two aims are not connected and even separately are quite weak. Several parts have already been worked out by others. Experimental plans lack rigor. • The timelines seem unreasonable.
GWG Votes	**Is the rationale sound?**
Yes: 3	• The rationale is sound though it depends on one or other of the loci being the key genotype and there is a lack of preliminary data to demonstrate that this is likely to be the case.
No: 7	• Overall idea is reasonable. • The assays are not validated, the rat model not ideal and the timelines unrealistic. The fact that they are going after only one risk allele in a complex multifactorial disease may not be the best approach. • The proposal lacks preliminary data to support that aim 1 genetic targeting can be successful. The protocol used to make RPE cells is outdated and hence the quality of RPE isn't that high. There is no data on quality of RPE isolated from organoids. Typically, this RPE is not mature or polarized. There is no data on surgical procedure for how they maintain RPE orientation when transplanting in RCS. Further RCS rats are not the right animal model for AMD or this work. • The work proposed has been done in many facets previously. • The rationale for aim 1 is reasonable. But for aim 2 the rationale is quite bad.
GWG Votes	**Is the proposal well planned and designed?**

Yes: 2	• There are technical challenges with the protocol which render the project difficult to achieve. Notably, the effective knockout at the identified locus; the efficacy of oxidative stress model and the quality of differentiation to RPE as described by the applicants.
No: 8	• The connection between aims 1 and 2 is unclear. Aim 1 is a disease in a dish model whereas aim 2 is about transplantation of RPE cells. AMD is not a monogenic disease. All evidence suggests there is no need to correct risk-alleles before transplantation. • It seems unnecessary to re-make cell lines that are already available. • Model choice is not well thought out, organoid model has been shown to fail. • Aim 2 is a weaknesses: not the right preclinical model. • Very ambitious with a timeline that is not feasible. • There is limited data on pitfalls. • Too many deliverables in a tight time line.
GWG Votes	**Is the proposal feasible?**
Yes: 4	• The work is challenging but feasible.
No: 6	• Challenges with the in vitro assays, choice of rat model and functional endpoints, assumptions and the ability to deliver/surgically insert a cell line in a single monolayer with the correct polarity are questionable. Timelines not feasible. • Aim 1 may not be doable. There is some evidence in the field that the genetic modification proposed here is not easily feasible. Aim 2 is feasible but not high quality. • Targeting of locus is difficult but lines are already available and the applicant should make use of it. • Surgically not feasible, model not sensitive enough to show effect, timelines are not reasonable, detail of oxidative challenge not provided. • They are using outdated methods.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 10	• There is a large unmet need. Especially for age related dry AMD. Stargardt's maybe a better choice for the clear genetic reasons. • Underserved communities may benefit from the approach.
No: 0	*none*