QUEST AWARDS

7/19/18

$19,007,245 GWG RECOMMENDED

$10,000,000 AMOUNT AVAILABLE

$0 BOARD APPROVED

							Score Range		Number of GWG Votes						
APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Resubmission	Previous CIRM Funding	Disease Indication	Product Type	Approach
DISC2-11131	Genetically Modified Hematopoietic Stem Cells for the Treatment of Danon Disease	$1,393,200	Y	95	94	2	90	97	14	0	N	Y	Danon disease	Cell therapy	Genetically-modified autologous blood stem cell transplant
DISC2-11157	Preclinical Development of An HSC-Engineered Off-The-Shelf iNKT Cell Therapy for Cancer	$1,404,000	Y	92	92	2	90	95	14	0	N	Y	Cancer	Cell therapy	Genetically-modified allogeneic natural killer T cell transplant
DISC2-11036	Non-viral reprogramming of the endogenous TCRα locus to direct stem memory T cells against shared neoantigens in malignant gliomas	$900,000	Y	90	90	1	90	95	14	0	N	N	Glioma	Cell therapy	Genetically-modified T stem cell memory cells targeting glioma
DISC2-10979	Universal Pluripotent Liver Failure Therapy (UPLiFT)	$1,297,512	Y	90	89	4	80	95	13	1	N	N	Liver-based metabolic diseases	Cell therapy	Genetically-modified allogeneic hepatic progenitor cells
DISC2-11105	Pluripotent stem cell-derived bladder epithelial progenitors for definitive cell replacement therapy of bladder cancer	$1,415,016	Y	90	89	4	79	95	14	1	N	Y	Bladder cancer	Cell therapy	hESC-derived bladder progenitor cells to replace pre-cancerous urothelium
DISC2-11192	Mesenchymal stem cell extracellular vesicles as therapy for pulmonary fibrosis	$1,393,200	Y	90	88	5	75	95	13	2	Y	N	Pulmonary fibrosis	Biologic	Vesicles from mesenchymal stem cells with anti-fibrotic potential
DISC2-11175	Therapeutic immune tolerant human islet-like organoids (HILOs) for Type 1 Diabetes	$1,637,209	Y	88	89	1	86	90	14	0	Y	Y	Type 1 diabetes	Cell therapy	hESC-derived immune-tolerant islet-like organoids
DISC2-10973	Small Molecule Proteostasis Regulators to Treat Photoreceptor Diseases	$1,160,648	Y	88	87	6	70	95	13	2	N	N	Photoreceptor diseases of the eye	Small molecule	Screen of small molecule compounds to correct photoreceptor pathology
DISC2-11070	Drug Development for Autism Spectrum Disorder Using Human Patient iPSCs	$1,827,576	Y	87	87	3	80	90	14	1	N	N	Autism	Small molecule	Screen for drugs that increase MEF2C in patient-derived iPSCs
DISC2-11183	A screen for drugs to protect against chemotherapy-induced hearing loss, using sensory hair cells derived by direct lineage reprogramming from hiPSCs	$833,971	Y	87	87	4	75	95	14	1	Y	N	Hearing loss	Small molecule screening tool	Screening tool for drugs that protect iPSC-derived sensory hair cells
DISC2-11199	Modulation of the Wnt pathway to restore inner ear function	$1,394,870	Y	86	85	3	75	87	13	1	N	Y	Hearing loss	Biologic (protein)	Study Wnt agonists that can stimulate hair cell regeneration
DISC2-11109	Regenerative Thymic Tissues as Curative Cell Therapy for Patients with 22q11 Deletion Syndrome	$1,415,016	Y	85	85	4	75	90	13	2	N	N	Chromosome 22q11 Deletion Syndrome	Cell therapy	hPSC-derived thymus organoid transplant for immune system restoration
DISC2-11107	Chimeric Antigen Receptor-Engineered Stem/Memory T Cells for the Treatment of Recurrent Ovarian Cancer	$1,381,104	Y	85	84	3	80	90	10	4	N	N	Ovarian cancer	Cell therapy	CAR-T cell therapy that targets ovarian cancer
DISC2-11165	Develop iPSC-derived microglia to treat progranulin-deficient Frontotemporal Dementia	$1,553,923	Y	85	83	4	75	90	9	5	Y	N	Frontotemporal dementia	Cell therapy	iPSC-derived microglia to treat progranulin deficiency
DISC2-11119	Preclinical pipeline development to generate autologous islet cell replacement therapy for pediatric patients with non-autoimmune diabetes	$1,269,199	N	80	80	3	75	90	1	14	N	Y			
DISC2-11150	Recruitment of endogenous Stem Cells for Blood Vessel Regeneration	$1,167,119	N	80	80	3	70	85	1	14	N	N			
DISC2-10959	Human pluripotent stem cell modeling to identify therapeutic strategies for the genetic disorder Pseudoxanthoma Elasticum	$1,404,000	N	80	79	6	70	88	4	11	N	N			
DISC2-11075	Label-Free Flow Cytometry for Purifying Stem Cell Derived Cardiomyocytes	$786,000	N	80	79	5	70	85	2	13	N	N			
DISC2-10970	Extracellular vesicles from endothelial progenitor cells as paracrine mediators of neurovasculotrophic repair of the retina	$1,827,576	N	75	75	2	70	80	0	15	N	Y			

DISC2-10985	A 3D in vitro immune-competent autologous perfused vascular network	$754,469	N	75	74	6	65	82	0	15	N	N			
DISC2-11169	Enhanced derivation of functional pancreatic cells from induced pluripotent stem cells by mechano-modulation	$573,534	N	75	74	11	50	90	2	13	Y	N			
DISC2-11180	Development of Stem Cell Therapy for Sanfilippo B	$899,999	N	75	73	3	65	75	0	15	N	N			
DISC2-11170	Oxygenated implant for insulin producing stem cells transplant to treat diabetes	$978,488	N	70	72	7	60	80	0	15	N	N			
DISC2-11176	Promoting myelin repair in Multiple Sclerosis via N-acetylglucosamine induced oligodendrocyte differentiation from neural stem/progenitor cells.	$1,123,282	N	70	71	7	65	84	0	15	Y	Y			
DISC2-11069	A new platform for discovery: deriving hPSC-derived spinal sensory INs and developing tracking methods to treat injured or diseased spinal cords	$778,440	N	70	70	1	70	75	0	15	N	Y			
DISC2-11089	A novel small molecule for mucositis/oral mucositis	$896,794	N	67	67	3	60	75	0	15	N	N			
DISC2-11182	Assessment of Novel Depots of Adipose-Derived Stem Cells for Chronic Rotator Cuff Injury	$1,305,770	N	65	67	6	60	75	0	15	Y	N			
DISC2-11002	A generic drug-discovery tool through phenotypic assays mimicking the early human development.	$500,000	N	65	63	9	50	75	0	15	N	Y			
DISC2-11094	Modulating Lgr5+ crypt stem cells by RSPO1 for the treatment of colitis	$1,384,700	N	65	63	4	55	70	0	15	N	Y			
DISC2-11202	Strengthening hematopoietic stem cell self-renewal program to improve transplantation	$1,404,000	N	-	-	-	-	-	0	14	N	Y			
DISC2-11141	Embryonic Stem Cells for Corneal Endothelial Dysfunction	$1,412,156	N	-	-	-	-	-	0	15	N	Y			
DISC2-11018	Development of USP16 inhibitors as therapy for Down's syndrome and/or age-related diseases.	$1,413,129	N	-	-	-	-	-	0	14	N	Y			
DISC2-11010	Developing a therapy to abrogate fibrosis-initiating progenitor cells in progressive organ fibrosis	$1,292,000	N	-	-	-	-	-	0	15	N	N			
DISC2-11019	Development of a novel therapeutic for Alzheimer's Disease targeting aberrant microglia function	$1,214,650	N	-	-	-	-	-	0	15	N	N			
DISC2-11068	IPSC-derived Endothelial cells for Treating Peripheral Vascular Disease	$1,412,613	N	-	-	-	-	-	0	15	N	N			
DISC2-11117	Stabilized Percutaneous Stem Cell Transendocardial Delivery Catheter	$641,345	N	-	-	-	-	-	0	15	N	N			
DISC2-11155	Induced Pluripotent Stem Cells for Ocular Surface Regeneration	$1,415,016	N	-	-	-	-	-	1	14	N	N			
DISC2-11164	Breast Cancer Post-Radiation Skin Injury Repair	$1,078,806	N	-	-	-	-	-	0	14	N	N			
DISC2-11115	Immuno-oncolytic Therapy Targeting Cancer Stem Cells of Glioblastoma	$1,256,754	N	-	-	-	-	-	0	15	N	N			
DISC2-11197	Highly Efficient Induction of Stem Cells to Endoderm	$795,000	N	-	-	-	-	-	0	15	N	N			
DISC2-11057	Characterization of a Novel Enzyme and Its Inhibitors in iPSC-Parkinson's Disease Models	$1,196,127	N	-	-	-	-	-	0	15	N	N			

Application #	DISC2-11131
Title (as written by the applicant)	Genetically Modified Hematopoietic Stem Cells for the Treatment of Danon Disease
Research Objective (as written by the applicant)	We propose to discover a novel, genetically modified hematopoietic stem cell based treatment for Danon disease, a rare lysosomal storage disease that affects the heart.
Impact (as written by the applicant)	As the only existing treatment for Danon disease is cardiac transplant, this therapy would significantly meet an unmet need. It also may help many other similar diseases.
Major Proposed Activities (as written by the applicant)	• Generation of ex vivo Genetically Modified Human HSPC Product (Month 1-6) • Functional Characterization of ex vivo Genetically Modified Human HSPC Product • Generation of Analogous Murine Product • In vivo Efficacy Evaluation of Analogous Murine Product in the Mouse Model of Danon Disease • Elucidate Purported Mechanism of Action
Statement of Benefit to California (as written by the applicant)	Danon disease is a fatal disease without cure, therefore the cellular treatment we plan to develop could directly benefit the citizens of California. Our findings may assist in the development of new treatments for other cardiac diseases. Thus the work also has the potential to help Californians who suffer from similar cardiac conditions. This project utilizes CA scientists and laboratories. With success, it will generate additional research and employment opportunities for CA citizens.
Funds Requested	$1,393,200
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 95

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	94
Median	95
Standard Deviation	2
Highest	97
Lowest	90
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• The stem cell technology proposed could provide a curative solution to patients with Danon disease. Similar technology could be extended to other genetic disorders. • Danon disease represents an unmet medical need. It is also the only human cardiomyopathy known to be caused by mutations in a lysosomal transmembrane protein. • The study is of high significance and impact.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 14	• Strong preliminary data support a sound rationale. • The rationale is sound and is based upon the previous success of this team in developing a similar approach to treating a another rare lysosomal disease. • Preliminary data show the transplantation of wild type HSPCs led to molecular, histological and functional rescue of a mouse model of Danon disease.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 14	• The applicant has presented a logical experimental plan with a stepwise progression to clinical application as well as a thorough investigation of the mechanism of action. • The project is very well thought out and all experiments are well designed. • The intent of the work is straightforward, which is to isolate HSPCs from Danon disease patients and transduce them to express the wild type gene. • Preliminary data demonstrate the ability of congenital wild type HSPCs to restore gene expression in knockout mice. • An appropriate retroviral vector has been developed to transduce expression of the wild type gene. • Potential pitfalls and the approaches to mechanistic investigation appear to be appropriately considered.
No: 0	*none*
GWG Votes	Is the proposal feasible?
Yes: 14	• All the necessary resources appear to be available to the team. • There are no concerns. All of the proposed milestones and expected project outcomes seem likely to be achieved within the proposed timeline. • This team has focused on the study and treatment of another rare lysosomal storage disease, and has been able to obtain the dramatic rescue of phenotypes using transplantation of wild type HSPCs. That work is progressing to submission of an IND for a phase 1 clinical trial using autologous genetically modified HSPCs. Thus, this team has experience in developing treatments for lysosomal storage disease.
No: 0	*none*

Application #	DISC2-11157
Title (as written by the applicant)	Preclinical Development of An HSC-Engineered Off-The-Shelf iNKT Cell Therapy for Cancer
Research Objective (as written by the applicant)	The expected outcome is a therapeutic candidate, allogeneic HSC-engineered HLA-I/II-negative human iNKT cells, that can potentially be used as an off-the-shelf cellular therapy for treating cancer.
Impact (as written by the applicant)	The proposed off-the-shelf HSC-engineered iNKT therapy has the potential to become a general cancer immunotherapy for treating multiple cancers and a large population of cancer patients.
Major Proposed Activities (as written by the applicant)	• Milestone 1: Production of the Universal HSC-Engineered iNKT (UHSC-iNKT) cells (1. Generate lentivector; 2. Generate CRISPR; 3. Collect HSCs; 4. Engineer HSCs; 5. Produce HSC-engineered iNKT cells.) • Milestone 2: Characterization of the UHSC-iNKT cells (1. Identity/activity/purity; 2. PK/PD; 3. MOA; 4. Efficacy; 5. Safety; 6. Combination therapy.) • Milestone 3: Delivery of the new therapeutic candidate (1. Identify UHSC-iNKT cells as the new therapeutic candidate; 2. Develop a draft TPP; 3. Prepare for and conduct a pre-pre-IND meeting.)
Statement of Benefit to California (as written by the applicant)	iNKT cells have the remarkable capacity to target a broad range of cancers independent of tumor antigen- and MHC-restrictions. The proposed HSC-engineered off-the-shelf iNKT cellular product has the potential to benefit a large population of cancer patients at California who suffer from cancers that are subject to iNKT cell regulation, including solid tumors (melanoma, colon, lung, breast, and head and neck cancers) and blood cancers (leukemia, multiple myeloma, and myelodysplastic syndromes).
Funds Requested	$1,404,000
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 92

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	92
Median	92
Standard Deviation	2
Highest	95
Lowest	90
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• The potential impact for a universal iNKT cell therapy for treating untreatable cancers is huge. • Using engineered NK cells could be used to treat a variety of cancers.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 14	• The plans to engineer the cells to make it universal is rational. The plans to eliminate the cells if they become toxic with targeting is rational. There is a potential role for these cells in cancer surveillance in epidemiologic studies. • The preliminary data is very strong and motivates the approach well.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 14	• The milestones, although challenging, are nicely outlined and the objective to get to a final cell to advance to translation is focused and disciplined. • Nearly all aims are well designed with appropriate alternate approaches specified.
No: 0	*none*
GWG Votes	Is the proposal feasible?
Yes: 14	• The milestones are doable and may be achieved within the proposed timeline. • The team seems to be well qualified to execute the proposed activities.
No: 0	*none*

Application #	DISC2-11036
Title (as written by the applicant)	Non-viral reprogramming of the endogenous TCRα locus to direct stem memory T cells against shared neoantigens in malignant gliomas
Research Objective (as written by the applicant)	We will develop a non-viral gene editing technology to replace the endogenous T-cell receptor alpha (TCRα) locus of stem memory T cells with transgene TCRs that are specific to brain cancer neoantigens.
Impact (as written by the applicant)	Gliomas are lethal tumors often affecting children and young adults. Therapy using Tscm directed to attack truncal neoantigens in these tumors may provide long-lasting protective immunity.
Major Proposed Activities (as written by the applicant)	• Establish and optimize the TCR replacement in CD8+ or CD4+ Tscm with H3.3K27M-specific or IDH1(R132H)-specific TCRs, respectively. • In vitro evaluation of TCR-replaced Tscm for their functional avidity in comparison to Tscm engineered with the conventional retroviral TCR vector and CRISPR-knock out of endogenous (e)TCR. • In vivo evaluation of TCR-replaced Tscm cells for anti-glioma effects in comparison with Tscm engineered with the conventional retroviral TCR vector and CRISPR-knock out of eTCR.
Statement of Benefit to California (as written by the applicant)	In children, brain tumors are the leading cause of cancer-related mortality and morbidity. Furthermore, IDH1-mutant gliomas tend to occur in young adults. Our institution is one of the largest brain tumor centers in the world, developing a number of innovative clinical trials and treating patients primarily from CA. The proposed study will establish a strong basis to develop a novel, safe and effective stem memory T cell therapy for patients with malignant brain tumors, including ones in CA.
Funds Requested	$900,000
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

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

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• Pediatric gliomas, such as diffuse midline gliomas (DMG) or diffuse intrinsic pontine gliomas (DIPG) represent an important unmet medical need in children. Such tumors have a median survival of less than one year. The majority of DMG and DIPG cases harbor a specific mutation that offers a potential tumor target for immunotherapy for pediatric gliomas. • The focus on pediatric patients could have a high impact. Gliomas and pediatric gliomas are an unmet medical need.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 14	• The preliminary data is excellent and motivates the proposal well. • The genetic modification of Tscms is very well thought out, as is the need to target mutation-derived antigens that are present in all tumor cells. The two proposed target antigens represent theoretically attractive targets.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 14	• The study design is elegant, with well constructed specific aims and a strong team. • This is a very well thought out project that has the advantage of having two mutation-derived antigens as potential targets. • They have developed a genome targeting system that permits a rapid and efficient insertion of DNA sequences to replace the endogenous TCR locus with a new TCR that redirects T cells to a cancer antigen. • Studies on T cells demonstrate relevant activity that resulted in inhibition of the growth of tumor cells in vitro for a month. The long term effectiveness of the approach needs to be tested further as the previous studies have been short term in nature, although the experimental models were carefully designed. • Data relevant to the safety of this approach with respect to the triggering of autoimmune attack on other cells of the brain is needed as epitope spreading is a concern. • The extent to which these therapies will overcome immunosuppression mediated by TGF-ß2 or other immune protective strategies of tumors should be considered.
No: 0	*none*
GWG Votes	Is the proposal feasible?
Yes: 14	• This is a well-designed timeline for the proposed activities. • It is good to empirically compare alternative methodologies and the proposal will compare viral, non-viral, and si-RNA knockdown methods. • The proposal to test two different antigen targets helps insure against a single failure.
No: 0	*none*

Application #	DISC2-10979
Title (as written by the applicant)	Universal Pluripotent Liver Failure Therapy (UPLiFT)
Research Objective (as written by the applicant)	Universal Pluripotent Liver Failure Therapy (UPLiFT) is composed of 2 lines- UPLiFT0 (from LiPSC-GR1.1) and UPLiFT1 which will be derived from gene edited universal human pluripotent stem cells.
Impact (as written by the applicant)	In some liver-based metabolic diseases, replacement of 5-10% of the liver mass may salvage the patient. Transplantation of hepatic progenitors from universal donor cells might avoid immunosuppression.
Major Proposed Activities (as written by the applicant)	• Developing and testing a cGMP-compliant manufacturing protocol for differentiating LiPSC-GR1.1 and the gene edited universal version of these cells into hepatic progenitors. • Production of sufficient cells of UPLiFT0 (LiPSC-GR1.1) and UPLiFT1 (Universal donor) sufficient to perform Milestones 3-5 including mouse studies. • UPLiFT Function and Fate: In our established in vivo model of hepatic stem/progenitor cell transplantation, assess the maturation, proliferation, and function of transplanted hepatic progenitor cells. • Select dose, determine regimen and route of administration. In tested model of hepatic failure establish effective dose and regimen. • Pilot preclinical safety/toxicology/long term outcomes at the optimal dose and route, assess off-target effects. • Preparation of Pre-Pre-IND package and scheduling/conduct a Pre-Pre-IND meeting.
Statement of Benefit to California (as written by the applicant)	California has the 12th highest death rate of liver disease in the US. The worldwide burden of liver disease is around 30 million patients, affecting one in ten in the US. Liver-based metabolic diseases are a rational starting point to apply cellular therapy to liver disorders. In some congenital metabolic disorders, replacement of 5-10% of the native liver mass may salvage the patient from the buildup of toxic metabolites. Our proposed cell therapy might expand treatment options.
Funds Requested	$1,297,512
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 90

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

Mean	89
Median	90
Standard Deviation	4
Highest	95
Lowest	80
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 scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• There is an important unmet need for improved methods to augment or replace liver transplantation. In the United States alone over 17,000 individuals are on the waiting list for liver transplants, while only about 5,000 transplants are performed annually. • The therapeutic impact could be potentially lifesaving for both adult and pediatric patients. • The proposal offers a novel approach to develop a universal donor pluripotent stem cell therapy to treat liver failure. This could be extremely impactful and address an unmet medical need. • The initial clinical target is severe genetically-caused pediatric metabolic liver disease. There has been marginal prior success with hepatic cell therapy, but no lasting cures and significant risk because of delivery route via portal vein (which would be exacerbated in therapy of conditions such as cirrhosis). 5-10% of liver function should suffice to treat many metabolic disorders.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 14	• The major pieces come together well to create a sound proposal. Good mouse data to show proof of concept in an animal system is already in place, using human cells in immunodeficient mice. • The applicant proposes to combine several approaches for which there is reasonable supportive evidence to create an innovative therapy. • The differentiation of human pluripotent stem cells through definitive endoderm to immature but functional hepatocytes should be capable of full maturation to achieve high level functionality in vivo. • The scaffold technology has ample precedent within tissue engineering methodologies developed over past two decades, though few successful human applications to date. • The genetic engineering designed to avoid immune rejection is not fully proven, but a reasonable approach for a universal donor cell and based on a strong collaboration with a corporate partner developing the technology.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 13	• The clearly laid out milestones are consistent with a development path leading to clinical trials. The applicant shows a sophisticated understanding of regulatory requirements with early lockdown of GMP-compliant manufacturing procedure, generation of large number of cells for each product under conditions that foreshadow future clinical application, and anticipation of FDA requirements for future clinical trials, e.g., release criteria, SOPs. • The applicant has appropriate assays for the functionality of product, demonstrates attention to dose finding, and proposes a critical test in an appropriate immune-deficient mouse model. • The proposal has a logical progression to initial long term studies in the mouse model with attention to key parameters for tumorigenicity, toxicology, and biodistribution. • Chronic expression of the HLA molecule could have unknown effects, however immunosuppression could overcome any concerns.
No: 1	*none*
GWG Votes	Is the proposal feasible?

Yes: 13	• Each component of the product is well conceived, and appropriate alternatives are available. Least certain may be the development of the universal donor cells. However, if unsuccessful, standard immunosuppression could still be used. • Excellent team with experience in both basic aspects of the study and development of comparable tissue engineered products. • The timeline with this team seems feasible.
No: 1	*none*

Application #	DISC2-11105
Title (as written by the applicant)	Pluripotent stem cell-derived bladder epithelial progenitors for definitive cell replacement therapy of bladder cancer
Research Objective (as written by the applicant)	We will 1) identify non-invasive bladder cancer patients with (pre)cancerous urothelium by single-cell RNA-seq and 2) replace this dangerous lesion with normal hESC-derived bladder progenitors.
Impact (as written by the applicant)	Replacement of corrupted (pre)cancerous urothelium with pluripotent cell-derived normal bladder progenitors will provide a definitive treatment for bladder cancer, expected to eliminate recurrence.
Major Proposed Activities (as written by the applicant)	• To develop a diagnostic surface marker assay to quantify the purity of hPSC-derived human bladder progenitor populations • To use single-cell RNA-seq to determine the purity of hPSC-derived human bladder progenitors and how closely they resemble primary human bladder cells • To test engraftment of primary mouse bladder stem cells, and eventually, hPSC-derived bladder progenitors, in injured mouse bladders • To profile (pre)cancerous bladder cells from patient samples and to develop diagnostic tools to monitor their spread using single-cell RNA-seq
Statement of Benefit to California (as written by the applicant)	Bladder cancer frequently recurs and progresses after treatment because of an extensive reservoir of (pre)cancerous cells that can serve as a source for development of new cancers. We propose to develop a stem cell-based cell replacement therapy to eliminate the devastating effects of bladder cancer recurrence and progression, and reduce the need for and expense of continuous patient monitoring. We also propose to develop methods to identify patients that would benefit most from such treatment.
Funds Requested	$1,415,016
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 90

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

Mean	89
Median	90
Standard Deviation	4
Highest	95
Lowest	79
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	1

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 15	• Bladder cancer is the ninth most common cancer worldwide with 200K deaths worldwide annually with frequent recurrence. There is a major need for curative therapy. • This is a highly innovative project that, if successful, would change how bladder cancer is treated. • The replacement of complete surgical bladder removal for patients with bladder cancer would be of great clinical impact. • The concept of chemical ablation and re-epithelialization of bladder from stem cell sources has the potential to improve patient outcomes by removing precancerous cells as well as tumors. • There are some concerns about the path to translation, including how ablation would occur in a human and whether catheter-based delivery is sufficient to engraft epithelial progenitors. • The details of how this cell replacement therapy would work in humans is not yet well understood. • It is not clear how the single cell RNA-seq data can be used to design a diagnostic.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 15	• The investigators have strong preliminary data demonstrating the ability to generate bladder progenitors and stratified cell types from hPSCs. • They have been able to make bladder progenitors from hPSCs and have a reasonable method for clearing out the bladder surface cells for subsequent replacement. • The investigators nicely show that a single clone of cancer can populate the epithelium of the bladder in mice. • The investigators have shown how they will differentiate PSCs to epithelial progenitors. • The single cell analysis in Aim 3 is fairly cutting edge, but is rapidly emerging as the best way to examine cancer cytology as the rarest cells may be the most informative. It doesn't appear that the team has much experience in this area, but their plan is simple and is likely to succeed.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 14	• Experiments are clearly designed to learn new information regarding the hPSC-derived bladder epithelial cells and evaluate their ability to regenerate ablated tissue in vivo. • It is unclear how the epithelium will be cleared out in humans. But there is a clear rationale for how they are treating the experimental mice to clear it out for transplantation with PSC derived progenitors. • Principal components may not be the best method for discriminant analysis, nor for exploration of clusters. The team should consult with clustering and machine learning experts before using principal components for this purpose. However, there is a good chance the signal will be strong enough that a suboptimal technique might be sufficient. • Consideration of pitfalls and alternative approaches is limited. There are some limited pitfalls listed for Aim 2 - namely a stepwise approach to cell ablation if mice are hurt too much. There are no alternatives for Aim 3 - it is unclear what happens if no differences are found with RNA-seq or clusters do not materialize as anticipated.
No: 1	• The translational product is not well-specified. There may not be any clear markers for a diagnostic that come out of the single cell RNA-seq analysis.
GWG Votes	Is the proposal feasible?
Yes: 14	• They may not achieve everything but they have a great team, great preliminary data, good rationale and a very important idea to improve patient care that is not being pursued by others. • There are clear, quantitative milestones for each of the aims. • This is a very strong team, they can cover expertise from start to finish: stem cell differentiation to urology translation including clinical trials.

	• There are some concerns that the ablation methods may not be effective. This would complicate analysis of the effects of the transplanted stem cell-derived cells. However, there is the general sense that depletion is ultimately a solvable problem. • It remains unclear whether the ablation of existing bladder epithelium is a solved problem. It was apparently unsolved last year as they failed to complete this aim in time frame of a prior CIRM award. However, in the intro to this current proposal they claim that both aims in the previous grant were completed, but they do not explicitly state that they have solved the problem of bladder depletion.
No: 1	• The scale of the single-cell RNA-seq experiments is not well-specified. There may be issues with sensitivity and sequencing depth if engraftment is lower than expected.

Application #	DISC2-11192
Title (as written by the applicant)	Mesenchymal stem cell extracellular vesicles as therapy for pulmonary fibrosis
Research Objective (as written by the applicant)	We propose to develop mesenchymal stem cell derived extracellular vesicles (MSC-EV) as treatment for lung fibrosis
Impact (as written by the applicant)	MSC-EV are promising for several lung diseases, but we need to better understand how they work, where they go in the body, and whether there is a subset of MSC-EV with better efficacy
Major Proposed Activities (as written by the applicant)	• To define the molecular characteristics, content, and effects of subsets of MSC-EV that do or don't express the Thy-1 protein • To define the distribution of Thy-1 positive and negative MSC-EV in the body in the setting of lung fibrosis, and define what cells they interact with • To compare the effectiveness of Thy-1(+) and Thy-1(-) MSC-EV in treating lung fibrosis of different causes, in comparison to existing treatments
Statement of Benefit to California (as written by the applicant)	There are estimated to be over 7000 individuals in California with idiopathic pulmonary fibrosis (IPF), an incurable and fatal disease. Current treatments only slow the disease progression, but do not cure IPF. Many of these individuals undergo lung transplantation which is very costly and at best adds a few years to life expectancy. Knowledge from this project may benefit other types of fibrosis such as liver fibrosis and heart failure.
Funds Requested	$1,393,200
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

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	5
Highest	95
Lowest	75
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	2

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 15	• Idiopathic pulmonary fibrosis (IPF) remains a devastating disease in critical need of new therapeutic approaches. The proposed approach utilizing MSC-derived EVs is not in itself completely novel as MSC-EVs are being explored in a range of other diseases including lung diseases. However, the proposed mechanistic approaches investigating the role of Thy-1 expressing MSC-EVs is novel and innovative in the context of IPF and has strong potential to lead to a new therapeutic possibilities. • Strong potential for clinical impact due to an unmet medical need. • The proposal focuses on an important disease.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 14	• The novel approach and well considered experimental studies have strong likelihood of leading to novel therapies for an otherwise difficult to treat disease. • The proposal is supported by strong preliminary data. • The proposal is supported by strong preliminary data and solid functional evidence.
No: 1	• The mechanism of action is not well-specified.
GWG Votes	Is the proposal well planned and designed?
Yes: 14	• The application is both well considered and logically presented. As a resubmission, the investigators have in particular responded well to critiques raised with the original submission. • The proposed methods are state of the art and utilize multiple models and systems for independent validation. • The experiments are well designed. The experiments have a high likelihood to dissect the underlying mode of action. • What is particularly noteworthy is the inclusion of different models of lung fibrosis in mice, notably focusing on potential resolution of established fibrosis rather than on inhibiting development of fibrosis which is what most of the existing literature on administration of MSCs in the bleomycin model does. • One additional thought for the investigators in milestone 2 would be to block Thy1 binding to resident lung cells using either anti-Thy antibody or integrin blockers and assess effects on biodistribution and effects of the MSC-EV administration. This would add further power to the proposed studies.
No: 1	• Activities do not elucidate the mechanism of action.
GWG Votes	Is the proposal feasible?
Yes: 14	• Preliminary data is supportive of all milestones and the appropriate techniques and technologies are in place. This suggests that the timeline for achieving the milestones is appropriate. • The plan is a bit overambitious for the timeframe proposed. • All aspects are supported well. The proposal is slightly ambitious for the proposed time frame.
No: 1	• The proposed work is too ambitious.

Application #	DISC2-11175
Title (as written by the applicant)	Therapeutic immune tolerant human islet-like organoids (HILOs) for Type 1 Diabetes
Research Objective (as written by the applicant)	Development of immune tolerant human islet-like organoids for transplantation into diabetic patients.
Impact (as written by the applicant)	Our proposal will progress the development of an unlimited, reproducible source of immune tolerant engineered islets for transplantation into Type I diabetics.
Major Proposed Activities (as written by the applicant)	• Demonstrate efficacy of immune tolerant HILOs in humanized diabetic mice • Demonstrate safety of immune tolerant HILOs • Incorporate a "kill switch" into immune tolerant HILOs
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 progress the development of functional islet-like organoids as an unlimited, reproducible source by engineering in immune tolerance to enhance and prolong functionality and survival upon transplantation into diabetic patients.
Funds Requested	$1,637,209
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 88

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

Mean	89
Median	88
Standard Deviation	1
Highest	90
Lowest	86
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• Human islet-like organoids have tremendous potential as a cellular therapy to treat type-1 diabetes. This proposal focuses on reducing immune rejection and engineering safety to the organoids. • Highly innovative cell therapy. • Excellent, novel approach to the major goal of developing an "off-the-shelf" product to provide functional pancreatic islet-like constructs for individuals with autoimmune diabetes. • Potential general solution to the problem of overcoming need for immunosuppression in allogeneic transplantation of stem cell-derived tissues/constructs.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 14	• Strong rationale; mature insulin producing cells make sense. • The project is based on outstanding work by this team and others in the field to generate mature, functional beta cells and islet organoids from human pluripotent stem cells. • The compelling preliminary data solidly support the ability of the islet organoids to improve glucose regulation in animal models of type 1 diabetes. • Outstanding preliminary data that demonstrates significant advances in the development of robust islet-like constructs and in the modulation of immune response to them. • Use of a "kill switch" is an important safety feature.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 14	• The revision has been rewritten and streamlined. • Aim 1 is well-designed to test the immune tolerance of the HILOs in humanized mice. • The safety assessment in Aim 2 is important to do, although it is difficult to assess safety based on a limited experiment. Looking deeper than teratomas is a strength. • The engineered kill switch in Aim 3 appears well designed and the evaluation plan is logical. • A clear development path is presented, with good use of sophisticated models for proof of concept and attention to safety as well as efficacy. • The applicant could pay greater attention to the question of whether the molecule is likely to protect against T cells directed against pancreatic antigen(s), in addition to overcoming surveillance against allogeneic transplants.
No: 0	*none*
GWG Votes	Is the proposal feasible?
Yes: 14	• The key experiments can be done in 2 years. • Milestone tasks are logical and well-aligned with project goals. • The team is excellent, with expertise in stem cell biology and diabetes. • Excellent team capable of executing an ambitious but well-conceived plan.
No: 0	*none*

Application #	DISC2-10973
Title (as written by the applicant)	Small Molecule Proteostasis Regulators to Treat Photoreceptor Diseases
Research Objective (as written by the applicant)	We will discover small molecule compounds that correct disease in eyecups (retinal organoids) differentiated from patient iPSCs with photoreceptor diseases.
Impact (as written by the applicant)	Our small molecule agents will provide new treatments for achromatopsia and cone-rod dystrophy. These are rare hereditary blinding diseases with no cures.
Major Proposed Activities (as written by the applicant)	• Transcriptomic and proteomic profiling of control and diseased iPSC-differentiated eyecups after ATF6 agonist treatment. • Define the potential for ATF6 agonists to improve photoreceptor protein folding and function in patient iPSC-differentiated eyecups. • Demonstrate that ATF6 agonists increase survival of patient iPSC-differentiated eyecups under ER stress and protein misfolding conditions. • Transcriptomic and proteomic profiling of control and diseased iPSC-differentiated eyecups after XBP1s agonist treatment. • Define the potential for XBP1s agonists to improve photoreceptor protein folding and function in patient iPSC-differentiated eyecups. • Demonstrate that XBP1s agonists increase survival of patient iPSC-differentiated eyecups under ER stress and protein misfolding conditions.
Statement of Benefit to California (as written by the applicant)	The proposed research will benefit the citizens of California by identifying new treatments for rare orphan vision loss diseases that currently have no cure. The proposed research will benefit the State of California by improving the visual acuity and color perception of California citizens with these diseases so that they can meaningfully engage in daily activities and pursue career and educational objectives with better quality-of-life outcomes.
Funds Requested	$1,160,648
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 88

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

Mean	87
Median	88
Standard Deviation	6
Highest	95
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	2

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• The use of disease-specific stem cell technology (retinal organoids) to identify novel therapeutic small molecule ATF6 agonists and XBP1 activators is highly innovative and could remove a critical bottleneck in the treatment of these retinal diseases. • The use of organoids to screen therapeutic compounds is innovative. • There is an outstanding potential for impact. The proposal is for identifying a targeted small molecule therapy attacking a gene defect in an orphan disease (retinal degeneration), but the therapy has potential for broader application.
No: 1	*none*
GWG Votes	Is the rationale sound?
Yes: 14	• The rationale is quite sound with good preliminary data. • The scientific premise is supported by publications and the preliminary data. The approach to screen for novel candidates in disease-specific retinal organoids is very logical. • There is strong preliminary data from the PI and collaborators identifying mutations and screening compounds to target affected proteins. • The applicant has an outstanding translational model developed from human patient-specific stem cells.
No: 1	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 13	• The project is extremely well planned and the experimental design will meet the criteria of the program announcement to achieve a candidate(s) to advance to translation. • The in vitro model is well developed and provides for detailed study of mutation and drug effects on retinal cells. • Two complementary pharmacologic strategies are explored.
No: 2	• Less cell lines are recommended; too many cell lines are proposed. • The screening methodology is not well described for the scale of studies proposed. • There are no alternate approaches if poor differentiation into eye cups occurs for any of the iPS cell lines.
GWG Votes	Is the proposal feasible?
Yes: 13	• The proposed milestones (6) indicate a very ambitious grant plan, and each of the milestones will require a substantial amount of work to complete. However, the group does have the expertise to complete the proposed work. • This is an extremely strong research team and the milestones/outcomes can be achieved within the timelines proposed. • This is an experienced team with synergistic expertise and experience working together. • The PI laboratory and core facilities provide access to key infrastructure, and the collaborator institution has the required elements for small molecule screening and development.
No: 2	• The scale of work is too high for the budget and timeline.

Application #	DISC2-11070
Title (as written by the applicant)	Drug Development for Autism Spectrum Disorder Using Human Patient iPSCs
Research Objective (as written by the applicant)	We will use human patient induced pluripotent stem cell (hiPSC)-based models to screen for a drug that activates a transcription factor critical to the treatment of Autism Spectrum Disorder (ASD).
Impact (as written by the applicant)	Our goal is to develop a small molecule to treat Autism Spectrum Disorder (ASD), which currently affects 1/68 children born in the USA. Currently, there is no effective treatment.
Major Proposed Activities (as written by the applicant)	• Assay Development for Drug Screening: Generate and characterize "disease-in-a-dish" models using hiPSCs generated from MEF2C Haploinsufficiency Syndrome (MCHS) patients, a form of ASD (month 1 - month 6). • High-throughput Screening: Screen for hit-to-lead compounds that upregulate MEF2 activity by reporter-gene assay (month 3 - month 9). • Efficacy Evaluation of Hits: Evaluate candidate therapeutics using ASD patient hiPSC-derived neurons (month 10 - month 18) • Drug Optimization - 1) Perform additional SAR and optimization, and 2) Perform additional CNS permeability studies and initial PK (month 18 - month 24). • Develop a Target Product Profile (month 21 - month 24). 1) Using the standard CIRM form, a TPP will be formulated for treatment of the MEF2C Haploinsufficiency Syndrome (MCHS) type of ASD.
Statement of Benefit to California (as written by the applicant)	Recent studies show that MEF2C activity not only affects MCHS but also other forms of ASD because MEF2C drives the activity of other ASD-related genes. Thus, while we are developing a treatment for the MCHS form of ASD, in fact MEF2 activator drugs may prove effective for a much large group of ASD patients. ASD is now reported to occur in 1 in every 68 births in both CA and the USA, so the benefit to the ASD community is potentially immense.
Funds Requested	$1,827,576
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 87

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

Mean	87
Median	87
Standard Deviation	3
Highest	90
Lowest	80
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	1

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 15	• ASD is a huge problem and the genetic approach here with MEF2C mutant iPSCs has potential. • The applicants have presented a very well thought out and designed proposal. By choosing to work in a comparatively rare disorder with implications in ASD, the applicants are in a good position to make unique and possibly high impact observations that could have consequences on a number of neurodevelopmental conditions. • Since other genetic causes of ASD have also been linked to altered MEF2c activity, any drugs identified may have larger implications for wider cases of ASD. • While ASD has clear unmet medical needs, this proposal does not consider some key issues that may arise when translating the hits from this screen to the clinic, largely centered around off-target effects as many of the hit compounds from such a screen seem likely to be global epigenetic transcriptional activators. • The potential biological mechanism through which any hit might act is not considered. Any hit that will specifically increase MEF2c expression may also affect unintended genes. Although a negative screen to identify such global effects is described, many hits may activate multiple but not all genes and so may be harder to catch in the negative screen.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 15	• The preliminary data presented in this proposal is of high quality and supports the work envisioned by the applicants. • MEF2c haploinsufficiency is linked to ASD. Increased expression of MEF2c is a worthwhile objective. Data included in the proposal shows that haploinsufficiency of MEF2c in human neural progenitor cells leads to increased excitatory neuron differentiation and hyperexcitability in neurons, at least when comparing one patient and one control. • The applicants have a good screening assay and a reasonable candidate to improve. • The proposal includes positive screening data yielding hits in a molecule family already found to be safe in humans, in particular a hit compound that shows a dose-dependent MEF2-enhancing activity in hiPSC-derived neural progenitor cells.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 14	• This is an extremely well-written proposal that considered many technical aspects of primary screening by using luciferase and secondary screening. • The thoughtful screening pipeline reflects the knowledgeable contribution of the med-chem team at the screening facility. Initial hits will be confirmed, tested for cell toxicity, and counter-screened to rule our non-specific transcriptional activation. • There is a risk that they will not find any single drug to activate MEF2c in ASD but the plans are well laid out. • The treatment plan for validation in iPSC derived neurons and progenitor cells was not clear. It was hard to determine if the applicants intended to use acute dosing at the 3 stated time points or if they intended chronic dosing beginning at the 3 different time points. This information is highly salient as there is a large difference between a therapy requiring acute and chronic dosing. • While discussing the potential off-target effects the only response provided was a reference to the expertise of the PI. A clearer description of a plan would have been preferable. • In the drug development section, a discussion of potential obstacles in developing blood brain barrier (BBB) permeability or low EC50 concentrations is not provided. BBB permeability is a

Application #	DISC2-11183
Title (as written by the applicant)	A screen for drugs to protect against chemotherapy-induced hearing loss, using sensory hair cells derived by direct lineage reprogramming from hiPSCs
Research Objective (as written by the applicant)	Development of a screen using inner ear sensory hair cell-like cells made by direct lineage reprogramming, for discovering drugs to ameliorate hearing loss during cancer chemotherapy.
Impact (as written by the applicant)	Hearing loss, both adult and pediatric, due to life-saving cisplatin chemotherapies. Lack of human inner ear hair cells for drug discovery purposes and disease modeling.
Major Proposed Activities (as written by the applicant)	• Develop and optimize induced human hair cell-like cell screening technology for cisplatin ototoxicity (Aim 1), for use in otoprotectant screening (Aim 2) and disease modeling (Aim 3). • Test previously identified otoprotectants (Vlastis et al., 2012) in human iHC screen with requisite otoprotective effects ("hits") against an LD50 dose of cisplatin (Aim 2). • Screen a 2500-compound library of FDA-approved drugs in human iHC screen for requisite otoprotective effects ("hits") against an LD50 dose of cisplatin. • Develop hair cell reporter lines from Cockayne Syndrome patient cells, and characterize human iHC disease models of cisplatin hypersensitivity in Cockayne Syndrome hair cells. • Test whether otoprotectants identified in Aim 2 confer protection against cisplatin ototoxicity in human iHC disease models of ototoxicity hypersensitivity.
Statement of Benefit to California (as written by the applicant)	Cancer in both children and adults is frequently treated with chemotherapy agents that have a high potential to damage hearing. When this occurs in children, significant developmental delays require expensive rehabilitation and special education. Since regeneration does not occur, adults are frequently left with permanent hearing loss. This proposal uses state-of-the-art stem cell techniques to develop a screen to discover drugs that prevent hearing loss due to life-saving chemotherapy.
Funds Requested	$833,971
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 87

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

Mean	87
Median	87
Standard Deviation	4
Highest	95
Lowest	75
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	1

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• Platin toxicity for cancer patients is a huge problem and the applicants have a unique model for use to screen for drugs to protect against this. • Development of a means of protecting sensory hair cells from ototoxicity with small molecules would be extremely important, and would also have potential implications from protecting against other aspects of cisplatin toxicity. • This seems like a good application of CIRM funds for an unconventional area.
No: 1	*none*
GWG Votes	Is the rationale sound?
Yes: 15	• The scientific rationale is fairly straightforward, which is to utilize iPSC-derived hair cells as a screening platform for identifying potential protective drugs. • The preliminary data on the ability to generate hair-like cells is very strong. • They have nice data showing that kinase inhibitors protect mouse and human hair cells from platin toxicity. • A small number of candidate protective agents have been identified and have been validated in both human and mouse cells. Whether these drugs are useful in vivo, and whether they also are protective of cancer cells, will be determined in the proposed research.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 15	• The proposal has a great model that is unique to an investigator with expertise in hair cell development and maintenance. • The project is well constructed. It is also biologically thoughtful, particularly in the context of the development of NER disease models. • The path through discovery and translation is well thought out.
No: 0	*none*
GWG Votes	Is the proposal feasible?
Yes: 15	• The applicant responded to the original reviews well. • The team is highly qualified for this work, and has added an appropriate advisor in response to previous criticisms. • The project design is appropriate, and the focus on drugs already approved for other purposes enhances the likelihood of the work being suitable for translation. • They have all the tools and support at their institution available to them.
No: 0	*none*

	major obstacle in all nervous system drug candidates and a more extensive discussion is needed.
No: 1	• It is unlikely that a small molecule can specifically upregulate a single gene. There is too much risk for this approach utilizing only a luciferase reporter system. There should be an alternate plan in case the hits cause off-target gene upregulation.
GWG Votes	Is the proposal feasible?
Yes: 15	• The applicants have shown that they can do the screen and have already made cells for the screen. • The proposed timeline is feasible especially taking into consideration that significant sections of the work have already been completed or currently underway. • The timeline is aggressive, particularly the case/control cohort generation, validation and phenotypic studies in months 1-6. • The applicant is an expert on MEF2c and its role in neurons.
No: 0	*none*

Application #	DISC2-11199
Title (as written by the applicant)	Modulation of the Wnt pathway to restore inner ear function
Research Objective (as written by the applicant)	We aim to identify drug regimens that stimulate endogenous progenitors in the inner to regenerate to restore hearing or balance functions.
Impact (as written by the applicant)	Treatment for irreversible hearing loss and balance disorders is limited, a drug regimen to reverse is highly impactful.
Major Proposed Activities (as written by the applicant)	• Production of R-spondin proteins • Drug testing in neonatal cochlear cultures • Drug testing in neonatal and mature utricle cultures • Drug testing in human utricle cultures • Drug testing in the cochlea in vivo • Drug testing in the utricle in vivo
Statement of Benefit to California (as written by the applicant)	Hearing loss (HL) is a permanent sensory disorder affecting about 48 and 7.7 million people in the US and California. Another 90 and 14.5 million US and California residents suffer from dizziness and vertigo. Currently, treatment options including hearing aids aim at improving the symptoms of HL and dizziness, yet fail to reverse the main underlying pathology, loss of inner ear sensory hair cells (HC). The current research aims to characterize a drug regimen to reverse these sensory deficits.
Funds Requested	$1,394,870
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 86

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

Mean	85
Median	86
Standard Deviation	3
Highest	87
Lowest	75
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 scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• Highly innovative proposal; the impact for cochlea regeneration would be enormous. • Significant unmet need for treatment of hearing loss and balance issues due to damage/degeneration of hair cells of cochlea & vestibular system. Wnt system agonist(s), particularly Rspondin, offer the potential to promote regeneration of relevant stem/progenitor cells.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 14	• Strong biological background. • Good preliminary data for regeneration driven by Rspondin in a murine system. The data suggest this protein should be safe. • Data in mature animals and evidence for comparable activity on human cells is needed and are the goals of this application.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 14	• Generally well-planned path to validate activity in appropriate murine models and on human cells (vestibular only) and to produce recombinant protein under conditions amenable to future scale-up. • A logical sequence of experiments is presented. • The criteria for the master cell bank and purification system that will be appropriate for subsequent GMP development should be made more explicit. • Greater clarity is needed on what the candidate will be - Rspondin only, or combination with Wnt. Single agent Rspondin would be much preferable for ease of development and probable safety. The plan should be better defined to show the criteria for the choice of actual candidate and preliminary dosing.
No: 0	*none*
GWG Votes	Is the proposal feasible?
Yes: 13	• The team is well equipped to do the research. • All major components are within competency of a strong, experienced team. • Goals appear achievable.
No: 1	*none*

Application #	DISC2-11109
Title (as written by the applicant)	Regenerative Thymic Tissues as Curative Cell Therapy for Patients with 22q11 Deletion Syndrome
Research Objective (as written by the applicant)	We propose a platform to generate transplantable thymus organoids derived from human pluripotent stem cells designed to treat severe immunodeficiencies in children affected by 22q11 Deletion Syndrome (22q11DS)
Impact (as written by the applicant)	Our product could impact 22q11DS and many other pathologies characterized by absence, degeneration or injury of the thymus and resulting in severe immunodeficiencies.
Major Proposed Activities (as written by the applicant)	• Implementation and optimization of conditions that lead to robust, pure, and efficient formation of Thymic Epithelial Cells (TECs) in 2D from human pluripotent stem cells, exploring signaling pathways. • Identify biomatrices and culture conditions to promote 3D thymus organoid formation, and test maturation of gene expression of functional thymus markers like FOXN1, Delta-like Notch ligands, AIRE. • Characterize at the molecular level in vitro derived TECs in comparison to fetal thymic tissues by RNASeq and ATASeq to study transcriptional regulation and chromatin openness and organization. • Defining and correcting the cell-intrinsic defects in 22q11 TEC ontogeny and identify potential drugs/pathways (e.g. Vitamin B12, retinoid acid) that could compensate for the thymic defects in 22q11DS. • Test transplantability and efficacy of thymic organids in vivo in nude athymic mice and assess T-cell maturation and reconstitution of TCR repertoire upon cotransplantation of hematopoietic stem cells. • Understanding sustainability and structural organization of the thymic organoid in vivo by assessment of growth, compartmentalization, maturation, and vascularization of the transplants.
Statement of Benefit to California (as written by the applicant)	Our objective is to develop a therapeutic product designed to treat children with 22q11DS and severe immunodeficiency (complete DiGeorge) with no access to allogenic thymic transplantation and urgent need for alternative therapies. These children, if not treated, have a life expectation of just two years. Our research will benefit the state of California and its citizens by significantly advancing the medical therapy and options for the community.
Funds Requested	$1,415,016
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 85

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

Mean	85
Median	85
Standard Deviation	4
Highest	90
Lowest	75

Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	2

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 15	• Developing new treatment options for DiGeorge Syndrome is significant. • Current treatment of DiGeorge syndrome is inadequate. Allogeneic thymus or thymic cells are probably the only path to an ultimate therapy. • This would address an unique unmet need with high risk and high reward. • There has been little research or development of induced thymic cells, so this is pioneering research.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 15	• The overall approach is well-justified. • Cell replacement therapy may help with the immune problems in the disease. Even if thymic stem cells end up engrafting ectopically, they could in principle provide some basic T-cell immunity. • The proposal would be improved if it had more preliminary data validating the differentiation protocol.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 13	• While the proposal is high risk due to the limited information on differentiation protocols, there is a high likelihood that if the investigators are successful important insights can be obtained. • There is a clear experimental outline. • 3D culture is advantageous. • The third aim is dependent on completion of earlier aims.
No: 2	*none*
GWG Votes	Is the proposal feasible?
Yes: 11	• The proposed experiments are likely to be successful even though high risk; the differentiation of cells into the TEC is unclear. • Team is very strong. If any team is capable of performing the proposed research, it is probably this team. • The candidate for translation could be better defined but there is optimism for the proposal. • The proposal is ambitious, so it is possible not all aims would be met. However, the project is worth a try.
No: 4	• The differentiation procedures are not completely worked out in the preliminary research. • The mouse model seems quite complicated and far from translational studies. • The work seems too ambitious for the timeline.

Application #	DISC2-11107
Title (as written by the applicant)	Chimeric Antigen Receptor-Engineered Stem/Memory T Cells for the Treatment of Recurrent Ovarian Cancer
Research Objective (as written by the applicant)	We are developing a tumor-associated glycan-targeting CAR-T cell with inducible cytokine production that drives T cell stem/memory phenotype and persistence for effective treatment of ovarian cancer.
Impact (as written by the applicant)	25% of ovarian cancer patients recur within 6 months. Targeting cancer stem cells with a persistent progenitor CAR-T cell product offers a potent strategy to address this recurrence.
Major Proposed Activities (as written by the applicant)	• Evaluate tumor associated glycan-specific CAR constructs using in vitro studies by varying extracellular and intracellular signaling domains to optimize for potency and selectivity • Evaluate multiple antigen-binding domains (i.e., scFv) within optimized CAR construct using in vitro studies. • Assess anti-tumor efficacy of lead CAR candidates in preclinical human xenograft models of serous ovarian cancer. • Generate a T cell activation-inducible cytokine production, comparing IL-12 and IL-15, for improved T cell functionality, stem/memory phenotype, and persistence using in vitro studies. • Optimize CAR-T cells with 'built-in' inducible cytokine production and identify lead CAR stem/memory T cell therapeutic product using in vitro studies. • Assess therapeutic efficacy of optimized CAR-T cells with 'built-in' inducible cytokine production in preclinical human xenograft models of serous ovarian cancer.
Statement of Benefit to California (as written by the applicant)	Ovarian cancer is the 5th most common cause of cancer mortality among women with ~10% of the annual diagnoses and ovarian cancer-related deaths in the US occurring in California alone. Fewer than 20% of advanced ovarian cancer patients survive past 5 years. This proposal aims to develop a targeted therapy for patients with recurrent ovarian cancer, which, if successful, would be a major advancement in the fight against this devastating disease and other aggressive cancers.
Funds Requested	$1,381,104
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 85

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

Mean	84
Median	85
Standard Deviation	3
Highest	90
Lowest	80
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	10
(1-84): Not recommended for funding	4

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• Generating CAR-T cells for ovarian cancer therapy is worth more attempts. It has not succeeded in the past, but a modified approach is presented here. • The focus on ovarian cancer is appropriate and could be of high impact.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 14	• Much of the proposal is well-considered. • The proposal uses sound genetic engineering strategies. • The stem cell targeting aspect of the proposal is weak. It is unclear how cancer stem cells can be developed from a cell line.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 12	• The investigator institution has a huge collective experience in this area. • The inducible approach is not novel and could have limited efficacy based on prior studies.
No: 2	*none*
GWG Votes	Is the proposal feasible?
Yes: 13	• The proposal is feasible. • The timeline is appropriate.
No: 1	*none*

Application #	DISC2-11165
Title (as written by the applicant)	Develop iPSC-derived microglia to treat progranulin-deficient Frontotemporal Dementia
Research Objective (as written by the applicant)	Develop stem cell-based therapy to treat dementia
Impact (as written by the applicant)	There are no treatments for dementia. If successfully achieved, this study will lead to a cure of a familial form of dementia in the elderly population.
Major Proposed Activities (as written by the applicant)	• Develop a robust human stem cell-derived microglial platform for cell-based therapy • Determine short-term safety and efficacy of engrafted human microglia in wildtype mice • Determine short-term efficacy of engrafted human microglia in frontotemporal dementia (FTD) mouse models • Determine long-term efficacy of engrafted human microglia in FTD mouse models
Statement of Benefit to California (as written by the applicant)	The proposed research will benefit the State of California and its citizens because of the potential to cure a major form of dementia in the elderly population. With the fast aging population in California, more and more Californians are diagnosed with neurodegenerative dementias. There is an urgent need to develop a treatment or cure for these devastating conditions. Success of our study will address this urgent medical challenge of our modern society.
Funds Requested	$1,553,923
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 85

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

Mean	83
Median	85
Standard Deviation	4
Highest	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 scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 13	• The proposal addresses a common form of dementia under 65 with no effective treatment and a relatively early onset. Familial FTD which is known to be caused by progranulin deficiency is rare but there is evidence that this pathway is important in other dementias. • Dementia is a significant clinical problem and an important unmet medical need. • Novel therapeutic approach.
No: 1	*none*
GWG Votes	Is the rationale sound?
Yes: 12	• The genetic cause is clear, and the microglial replacement strategy is validated in preclinical studies. • Better data on the yield of microglia from differentiation protocols is presented in this revised application; scale-up of the cells should be possible. • Outstanding preliminary data.
No: 2	• It is unclear whether enough cells be generated at the time point should they be transplanted.
GWG Votes	Is the proposal well planned and designed?
Yes: 14	• The applicant presents a robust differentiation protocol and good characterization of cellular product. The studies include short and long term efficacy studies along with toxicity. Functional assessment including electrophysiology and behavioural studies rounds out the characterization of the product. • The panel still had some concerns about feasibility of scaling up to the number of cells required for human therapy. The number of cells required for human therapy is unclear. However, proof of principle may be sufficient to justify funding at this stage. • No weaknesses noticed.
No: 0	*none*
GWG Votes	Is the proposal feasible?
Yes: 13	• PI has extensive experience in this field. The consultant provides invaluable experience. Other experts in electrophysiology and stem cell transplantation into CNS round out the team. • The project has translational potential.
No: 1	*none*

Application #	DISC2-11119
Title (as written by the applicant)	Preclinical pipeline development to generate autologous islet cell replacement therapy for pediatric patients with non-autoimmune diabetes
Research Objective (as written by the applicant)	To prove that gene edited stem cell-derived islet cells can be safely and effectively used to treat diabetes
Impact (as written by the applicant)	We expect that this project can serve as a model for developing new treatments for patients with non-autoimmune diabetes.
Major Proposed Activities (as written by the applicant)	• To create a new process that produces sufficient numbers of cells to treat diabetes in rats • To evaluate if transplanting patient-specific stem cell-derived insulin cells under the skin or in the fat is as effective as other transplantation sites • To test if patient-specific stem cell-derived insulin cells can regulate blood sugar in diabetic rats • To evaluate if transplanting patient-specific stem cell-derived insulin cells is safe • To meet with the FDA at the conclusion of the study and earn their support to move forward into the next phase of pre-clinical trials
Statement of Benefit to California (as written by the applicant)	California is already a leader in advancing stem cell technology. If we are successful, we believe that California can become the center for patients with non-autoimmune of diabetes to come to for treatment.
Funds Requested	$1,269,199
GWG Recommendation	(1-84): Not recommended for funding

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	90
Lowest	75
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 scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 13	• Non-immune diabetes offers an opportunity to demonstrate the value and potential of stem cell therapy. • Good concept to treat individuals with genetically-caused, non-autoimmune type 1 diabetes with insulin-producing cells derived from iPS cells corrected for the genetic defect. • The work could address key bottlenecks in translation with an autologous product. • This proposal is of significance, but the translational aspect is not fully developed. • Preliminary data and performance on previous grant is strong.
No: 2	*none*
GWG Votes	Is the rationale sound?
Yes: 14	• Numerous groups have shown that beta cell progenitors can be derived from human pluripotent stem cells. • The idea and concept seems focused and based on sound preliminary data: derivation, analysis, genetic correction of the gene mutation.
No: 1	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 7	*none*
No: 8	• Goal of establishing 3 further patient-derived iPS lines representing different defects (2 of which require genetic correction) is clear and follows plan established under a previous CIRM award. • The plan does not include sufficient attention to what is already known in the field about difficulties of achieving high quality pancreatic islet-like iPS cell-derived tissue in vivo. Analysis seems largely limited to measurements of insulin & c-peptide and physiological glycemic control. A greater understanding of the cell & molecular biology of the developed constructs is needed. • Experimental endpoints are not well-developed. A better understanding of the milestones and metrics for achieving them are needed. • The collaborative plan within the team is not strong enough to enable translation. The scale-up aspects of the work need quantitative milestones. • The development plan has insufficient attention to future GMP, scale-up, regulatory aspects within the context of a Discovery program project.
GWG Votes	Is the proposal feasible?
Yes: 12	• The work seems feasible with the 2-year timeline.
No: 3	• There are some concerns about the composition and role of the research team. • Talented young PI, but needs much better integration with development team. Other faculty members of team do not address this well. A heavy reliance on core lab and CRO is fine, but a proposal with a more sophisticated understanding of what actually is required to advance a product through development & regulatory stages is needed. • Developing a successful islet-like transplant from human iPS cells in vivo remains challenging, and the application does not seem to reflect state-of-the-art in this field.

Application #	DISC2-11150
Title (as written by the applicant)	Recruitment of endogenous Stem Cells for Blood Vessel Regeneration
Research Objective (as written by the applicant)	A decellularized native matrix as vascular grafts that have anti-thrombogenic activity and regeneration capability by recruiting endogenous stem cells/progenitors
Impact (as written by the applicant)	This approach will enable efficient fabrication of decellularized grafts, circumvent the manipulation of cells in vitro, and harness the regeneration potential of endogenous stem cells/progenitors
Major Proposed Activities (as written by the applicant)	• 1.Fabrication and the mechanical / chemical characterization of decellularized fibrotic conduits as vascular grafts • 2. Investigate the bioactivity of endothelial progenitor-capturing peptide in vitro and in vivo • 3.Determine the performance of immobilized SDF-1 on heparin for stem cells recruitment in vitro and in vivo • 4.Determine the combined effects of cell recruitment and capturing in vitro and in vivo
Statement of Benefit to California (as written by the applicant)	Over 20 million Americans have coronary or peripheral artery diseases. In addition, ~450,000 patients with kidney failure are subjected to weekly hemodialysis and need vascular access grafts with long-term stability. Currently, bypass procedure remains a key treatment for many patients with severe artery clogging. However, small-diameter vascular grafts with long-term patency are not available. Our work will address this unmet medical need and benefit these patients.
Funds Requested	$1,167,119
GWG Recommendation	(1-84): Not recommended for funding

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	● Improved small diameter vascular grafts have the potential to impact coronary and peripheral artery disease. ● The proposed product incorporates several novel and innovative design concepts for a small diameter vascular graft, including biodegradation, anti-thrombotic coating, and endogenous cell recruitment. ● The concept, if successful, would have significant impact for patients.
No: 1	*none*
GWG Votes	Is the rationale sound?
Yes: 13	● The graft is well-designed to resist thrombosis prior to endothelialization and to recruit endogenous cells. ● The preliminary data regarding peptide binding to endothelial cells is strong. ● The concept is exciting, based on significant preliminary data.
No: 2	● The potency of peptide for capture is unclear, as well as questions about scalability and possibly inadequate cell characterization.
GWG Votes	Is the proposal well planned and designed?
Yes: 9	● In vitro and in vivo characterization plans are comprehensive and clear.
No: 6	● Translational hurdles due to consistency and immune response with a xenogenic product need more substantial attention in the experimental plan. ● The numbers of cells and the required affinity for the peptide need to be clearly specified.
GWG Votes	Is the proposal feasible?
Yes: 12	● The graft is well-designed to resist thrombosis prior to endothelialization and to recruit endogenous cells. ● Quantitative success criteria would strengthen the proposal. ● The set of experiments is logical, but need to be refocused towards specific translational barriers.
No: 3	*none*

Application #	DISC2-10959
Title (as written by the applicant)	Human pluripotent stem cell modeling to identify therapeutic strategies for the genetic disorder Pseudoxanthoma Elasticum
Research Objective (as written by the applicant)	Small molecule or biologic for the treatment of the orphan disease Pseudoxanthoma elasticum (PXE), using human pluripotent stem cell modeling of 'disease in a dish'
Impact (as written by the applicant)	PXE is an incurable genetic disorder characterized by progressive calcification of the skin. Using hPSCs, we for the first time identify new drugs/biologics for treating PXE.
Major Proposed Activities (as written by the applicant)	• Screening of lead small molecule candidates for inhibiting ENPP1 in hPSCs • Screening of recombinant antibody clones for inhibiting ENPP1 in hPSCs • Identification of lead candidates that most potently inhibit calcification in hPSC model of disease • Identification of recombinant antibody clones that most potently inhibit calcification in hPSC model of disease • Further screening of small molecule candidates and biologics for off target effects against other ENPP members • Demonstration of efficacy in small animal model with chosen small molecule/biologic to identify single candidate for further development
Statement of Benefit to California (as written by the applicant)	PXE is a genetic disorder caused by mutations in the gene ABCC6, occurs in the general population at a frequency of 1/50,000-1/150,000 individuals and is characterized by progressive calcification of soft tissues. There are no effective means to treat this condition. Residents of California also suffer from this condition. The rarity of the disease and suboptimal murine models have impeded discovery of therapies. Using hPSC models, we identify novel therapeutic candidates for PXE..
Funds Requested	$1,404,000
GWG Recommendation	(1-84): Not recommended for funding

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	6
Highest	88
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	4
(1-84): Not recommended for funding	11

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• The need to develop new treatment options is clear. • The goal is to use an iPSC disease in a dish model to screen compounds and antibodies, which could produce high-impact lead candidates for translation.
No: 1	*none*
GWG Votes	Is the rationale sound?
Yes: 13	• The rationale is built on exciting preliminary data. • The gene ENPP1 is overexpressed in ABCC6 mutant cells, and small molecule inhibitors of ABCC6 have been identified that can alleviate calcification in mice and in iPS-derived cells. • A mouse model of PXE shows that calcification can be alleviated with ENPP1 inhibitors. The human iPS model is attractive to supplement the mouse data and expand the research into ENPP1 inhibitors. • The study design is well presented, however there are some concerns related to the stem cell model. It is not clear whether the phenotype selected is disease relevant as the cell lines are not generated from patients.
No: 2	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 8	• The goal to evaluate the effectiveness of small molecule inhibitors of ENPP1 and also antibodies specific for ENPP1 in the iPS cell culture model to see if they can inhibit calcification is sound.
No: 7	• The mouse model seems to work well and therefore the work with human iPSCs may not be necessary. • There needs to be a stronger link between the phenotype in the cell model and how it links to patient and disease phenotype. • The screening characteristics need to be described for the follow up experiments. For example, a Z-prime for the proposed readout will be important. • The validation work with patient iPSCs is not well specified. Alternate approaches are not well formulated.
GWG Votes	Is the proposal feasible?
Yes: 12	• The work is feasible, but the work needs to be packaged better to enable the reviewers to better understand the exact activities. • This group is positioned to meet the reasonable outcomes proposed.
No: 3	*none*

Application #	DISC2-11075
Title (as written by the applicant)	Label-Free Flow Cytometry for Purifying Stem Cell Derived Cardiomyocytes
Research Objective (as written by the applicant)	We will develop a label-free, non-genetic flow cytometer that can purify stem cell derived cardiomyocytes (SC-CMs) and isolate cells by maturity and subtype (atrial, ventricular, pacemaking).
Impact (as written by the applicant)	Purification of stem cell derived cardiomyocytes is a major challenge. Obtaining purified cells with defined maturity and subtype can improve tissue engineering for stem cell therapy and drug testing.
Major Proposed Activities (as written by the applicant)	• Build a proof of concept second harmonic generation (SHG) flow cytometer with microfluidic devices, an optical method for cell sorting, and a unique laser design for generating SHG signals from cells. • Determine the specificity of SHG signals to identify SC-CMs and to differentiate cells based on maturity and subtype (atrial, ventricular, pacemaking). • Determine theoretical maximum analytical throughput for SHG analysis of SC-CMs in flow by extrapolating data on flow rates and SHG signal intensity. • Assess cell viability and function of SHG sorted cells. Viability will be based on commercial assays, and function is based on optical recording of action potential. • Demonstrate reduced incidence of arrhythmias in purified cell populations and improved performance of purified cells to detect drug induced arrhythmias.
Statement of Benefit to California (as written by the applicant)	Heart disease and the high costs of drug development (due to drug attrition from cardiotoxicity) are major health issues. SC-CMs are a promising source of heart cells for stem cell-based therapies to treat patients and cardiotoxicity screening of drugs. A major roadblock in using SC-CMs for these applications is the lack of a method to purify these cells. The proposed technology will allow for pure SC-CMs to be used to engineer heart tissues with the proper function for these applications.
Funds Requested	$786,000
GWG Recommendation	(1-84): Not recommended for funding

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	85
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 scientific 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	• If successful, this approach could help produce higher purity CMs. • The proposal should mainly focus on the impact for non-regulated medical approaches.
No: 4	• The significance in terms of translation is unclear. Although purification is key, there are more pressing issues associated with cell therapy for cardiac diseases. • It is unclear how this method would be advantageous compared to using FACS or MACS for cell therapies.
GWG Votes	Is the rationale sound?
Yes: 12	• The proposal builds on the assumption that the proposed measurement is a good surrogate to sort CMs, but is not well-supported. More data addressing this concern would substantially improve the proposal. • The benefits and feasibility of using the proposed novel methodology are unclear. Purification methodologies already established for cell transplantation, such as FACS and MACS can be used. • This may be a valuable way to purify cardiomyocytes at different stages of maturation, though the translational value is unclear.
No: 3	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 9	• The proposal is well-designed.
No: 6	• The rationale for proposed time points during differentiation is unclear. • The experiment description needs more detail.
GWG Votes	Is the proposal feasible?
Yes: 9	• The investigators are well-qualified. There is a high likelihood that the proposed milestones can be achieved.
No: 6	• This is a good exploratory grant but not feasible for a 2-year grant. • The timeline is overambitious for a 2-year grant. Success criteria of 95% may not be feasible in Milestone 4.

Application #	DISC2-10970
Title (as written by the applicant)	Extracellular vesicles from endothelial progenitor cells as paracrine mediators of neurovasculotrophic repair of the retina
Research Objective (as written by the applicant)	Extracellular vesicles from human umbilical cord blood-derived endothelial progenitor cells (EPCs) as agents for the neurovasculotrophic repair of ischemic and neurodegenerative retinopathies
Impact (as written by the applicant)	1. Demonstration of the safety, mechanism, and efficacy of a novel therapeutic for ischemic and degenerative retinopathies 2. Characterization of EV isolation protocol scalable to meet clinical demands
Major Proposed Activities (as written by the applicant)	• Assess the neurovasculotrophic effect of CD44hi ECFC-derived EVs by quantifying their activity in rescuing murine models of retinal vasculopathy and neurodegeneration • Characterize and test EVs harvested from conditioned media using a novel isolation protocol to assess the scalability, reproducibility and the effects of storage on harvesting therapeutic EVs • Determine the histocompatibility and immunogenicity of intravitreally injected EVs from CD44hi ECFCs • Characterize the retinal and systemic biodistribution of EVs to investigate the in vivo fate of injected EVs • Identify possible intravesicular agents facilitating CD44hi EV-mediated neurovasculotrophic effects • Investigate the paracrine mechanism underlying the therapeutic effects of CD44hi EVs
Statement of Benefit to California (as written by the applicant)	The leading cause of vision loss in Americans under the age of 55 is diabetic retinopathy. A recent study estimates that 9% of Californians suffer from diabetes, an additional 46% have pre- or undiagnosed diabetes and, worldwide, there are over 3.3 million diabetic individuals with vision loss. Our research has the potential to significantly reduce, or restore, vision loss in these patients as well as others suffering from retinal diseases like glaucoma and retinal degeneration.
Funds Requested	$1,827,576
GWG Recommendation	(1-84): Not recommended for funding

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	2
Highest	80
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific 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 ECFC-EVs have the potential to offer a novel progenitor cell technology that would improve treatment of ischemic neurovascular conditions and overcome the current limitations in current treatment options. • This approach is unique, novel and holds significant potential for treatment. • The preliminary data presented is sound and provides a basis for the work outlined in this proposal. • The applicants have several previously published studies that pave the way to conduct this study and bring it to successful conclusion.
No: 4	• The impact of these studies is unclear as it is a repetition of studies performed with ECFCs.
GWG Votes	Is the rationale sound?
Yes: 11	• The proposal is thoughtfully designed, building on solid foundations of the collaborators, previous studies and expertise. • The PI presents extensive and compelling preliminary data that EVs from CD44hi ECFCs have potent neurovascular rescue activity in rodent models of ischemic retinopathy and neurovascular degeneration. • The basis for activity is still unclear; a better comparison of cells & exosome activity is needed. The role of CD44 functionally and whether there is a mechanistic relationship to the desired activity is unclear. • The idea is very interesting but there are some significant concerns with the design of the study.
No: 4	• It would have been preferable if data was provided to show that EVs are superior in outcome than ECFCs, which is proposed in Milestone 6.
GWG Votes	Is the proposal well planned and designed?
Yes: 10	• From the preliminary data, there still appears to be a rather large amount of cell death in the CD44hi condition. This needs to be addressed as it likely to impact the outcome of the study. • The project is well designed but represents an incredible amount of work to be completed within two years. • The experimental design is logical and the PI has all the techniques and models developed. Slight caution should be given for the retinopathy model which is a developmental model rather than a model for ischemic vascular disease in adults. • The applicants also provide limited rationale as to why they selected to perform studies on a glaucoma model as the previous work they cite is based on EVs derived from a different cellular population than the ones utilized in this study. It would have been useful to have this further explained. • It is unclear whether there is inclusion of control animals in the mice studies. The proposed groups include EVs derived from CD44hi, CD44low, and PBS but only for the transgenic animals. • It is unclear why the applicants elected to perform tests screening the effect of different storage conditions in mice when they have a functional in vitro assay, given the added time, expense, and utilization of animals associated with work in vivo. Cell culture results could be confirmed in mouse models. • A rationale is needed for why 5 and 24 hours were selected to determine where the EVs end up. The proposed time points seem like rather short for determining systemic spreading of a compound that is injected into the eye.

	• The PI addresses many of the potential limitations and offers alternative approaches which are acceptable. However, there is concern about donor variability in the cord blood samples and a better approach would have been to start with iPSC-derived ECFCs which are being successfully generated in many labs.
No: 5	• Overambitious for a 2-year grant.
GWG Votes	Is the proposal feasible?
Yes: 5	• Preliminary data shows feasibility.
No: 10	• The milestones and project outcomes are logical and clearly presented. However, it is doubtful the investigators will achieve all they propose. • The grant timeline is over ambitious.

Application #	DISC2-10985
Title (as written by the applicant)	A 3D in vitro immune-competent autologous perfused vascular network
Research Objective (as written by the applicant)	We will create an "organ-on-a-chip" comprised of a 3D perfusable vascular network, derived solely from the same pluripotent stem cell source, that simulates important features of the immune response.
Impact (as written by the applicant)	A current limitation in the development of precision medicine is the lack of model systems that can predict or simulate the patient-specific immune response in diseases such as Type I diabetes.
Major Proposed Activities (as written by the applicant)	• Create four (4) new induced pluripotent stem cell lines and the corresponding genetically matched lymphocytes from peripheral blood. • Create four (4) new iPS-derived endothelial cell lines from the iPS lines in Activity/Milestone #1. • Create four (4) new iPS-derived myofibroblast cell lines from the iPS lines in Activity/Milestone #1. • Create 3D perfused vascular networks in a microfluidic device, each derived from a singular pluripotent stem cell source (iPS lines and cells from Activities/Milestones #1-#3). • In vitro observation of extravasation and activation of patient-derived lymphocytes from the autologous (subject-matched) perfused vascular network and within the extracellular matrix, respectively.
Statement of Benefit to California (as written by the applicant)	The proposed platform technology will be commercialized by a California start-up company founded by the investigators. The growth of this company in the field of precision medicine will bring high quality employment opportunities and tax revenue to California. In addition, the advances in precision medicine should provide new treatment opportunities to the residents of California in such prevalent diseases as cancer, diabetes, and rheumatoid arthritis.
Funds Requested	$754,469
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 75

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

Mean	74
Median	75
Standard Deviation	6
Highest	82
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 scientific 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 work proposed here has the potential to open new avenues of research to address a number of fundamental and disease oriented questions. The 3D vascularized organoids being proposed here have a large degree of adaptability and can be tailored to suit the multiple research questions. Thus, the successful completion of this work will fulfill an unmet need in fundamental and medical research. • The product could be used as a model system in which to study aspects of immune function and cancer immunology.
No: 7	• It is difficult to grasp the significance as well as the long-term implications of these studies. The applicant is unclear in terms of future goals, and does not clearly state the applicability of the system. • The translational impact of the project is unclear as the relevance of the system is not clearly defined.
GWG Votes	Is the rationale sound?
Yes: 8	• The preliminary data presented in this work is sound and very convincing. • The proposal does not address how they plan to translate the successful completion of their milestones to a clinical setting. It would be very important to discuss how the applicants plan to achieve translation of their technology given that their work needs quite a bit of scaling and large-scale reproducibility, as well as costs involved in making patient-specific 3D in vitro systems.
No: 7	• It is difficult to grasp the significance and the long-term implications of these studies. • The rationale of collecting donor bone marrow to generate iPS cells and then differentiate these in cell types present in the bone marrow is unclear.
GWG Votes	Is the proposal well planned and designed?
Yes: 7	• Potential pitfalls are discussed in detail. However, it is unclear what would happen if participants had cell counts outside of the normal range. • More details regarding the subjects from whom the cells will be derived should be provided (healthy controls, matched for age, etc). • The proposal would benefit from a discussion of the other cell types that are expected to be present as they aim for 95 or 90% purity. It is unclear if the applicant plans to determine what other cells are present and the potential consequences of different cell populations. • The screening procedures should be more thoroughly described.
No: 8	• This grant is aimed mostly at producing a new research model and platform system. Though it would be useful for more goal-driven research, the end result of this grant is more of a starting point for future studies that would address specific unmet medical needs. • A rationale is needed for the initiating cell choice of bone marrow aspirate.
GWG Votes	Is the proposal feasible?
Yes: 13	• The milestones and timeline look good. • The applicants have the expertise to bring this proposal to completion. The PI and co-PI have a long-standing and productive collaboration. • The timeframe of the proposal is ambitious.
No: 2	*none*

Application #	DISC2-11169
Title (as written by the applicant)	Enhanced derivation of functional pancreatic cells from induced pluripotent stem cells by mechano-modulation
Research Objective (as written by the applicant)	This study will develop a stem cell culture technology which will improve the differentiation efficiency and downstream functionality of stem cells for enhanced therapeutic applicability.
Impact (as written by the applicant)	It will improve current inefficient stem cell differentiation methods to produce clinically functional cells for enhanced therapeutic applications.
Major Proposed Activities (as written by the applicant)	• Optimize stem cell culture scaffolds for enhanced functionality and biocompatibility • Develop a high-throughput cell culture system with on-demand mechanically tunable scaffolds • Determine the optimal protocol for stem cell differentiation towards insulin-producing cells • Examine the functionality of the derived pancreatic endocrine cells
Statement of Benefit to California (as written by the applicant)	This project seeks to advance the effectiveness of the use of stem cells for regeneration of damaged tissues in patients by developing a novel technology. The project speaks directly to the mission of CIRM, particularly to improve the human health of California's rapidly growing population by advancing stem cell-based therapies. The commercialization of the full-scale system would benefit the people in California with the financial impact of increased employment and tax revenues.
Funds Requested	$573,534
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 75

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

Mean	74
Median	75
Standard Deviation	11
Highest	90
Lowest	50
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	2
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific 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	• Current protocols for differentiation of stem cell into beta cells for replacement in autoimmune diabetes are suboptimal. They require in vivo implantation to promote full differentiation and there is lots of batch-to-batch variability which is an issue for clinical translation. Improving protocols for differentiation of stem cells into insulin-secreting cells before implantation will decrease the variability of current cell products and increase translatability to humans. • The applicants present an original approach to a neglected aspect of the stem cell environment. Evidence exists that stiffness of microenvironment can strongly influence stem cell renewal and differentiation through multiple downstream steps. Providing dynamic regulation of stiffness of culture substrate may (i) increase differentiation yield of stem cells into beta cells and other islet cells and (ii) improve functionality of differentiated beta cells. • This novel method to regulate/drive differentiation through multiple stages has broad potential impact. However, the proposal is dense and difficult to follow, diluting the significance and novelty of the platform. • More consideration has been given to the scale-up of the technology and to downstream applications in this revised proposal.
No: 5	• There are some concerns about the impact of the research for medical outcomes. This is a very technical grant, but the impact on relevant medical outcomes is unclear. • The work is too early stage and needs much more development before embarking on translational studies.
GWG Votes	Is the rationale sound?
Yes: 11	• The applicants present strong data on role of tissue stiffness during pancreatic development and strong preliminary data on cell maturation. Preliminary data show 10-fold increase in stem cell differentiation efficiency and in beta cell functionality by modulating substrate stiffness. However, effects of substrate stiffness on stem cell differentiation and on beta cell function has been shown using a different platform than what proposed in the grant. • Data showing that substrate stiffness affects differentiation of stem cells into beta cells and functionality of differentiated beta cells are convincing, as well as data showing that substrate stiffness can be modified, and data showing collagen does not affect stiffness properties. • It is not clear which ones of the proposed technologies will be translated first. • It is unclear how much optimization of the 96-well culture system is needed before testing. It is briefly mentioned that the maximum applied voltage should not be higher than 1.0 V to prevent electrolysis but the simulation results show that 3.8V are necessary to produce the changes in stiffness that are necessary for the study. • The 6-well plate seems to be necessary for clinically relevant expansion of stem cell-derived beta cells but the system is based on different principles for substrate stiffness than the 96-well system and no preliminary data are provided to show feasibility of this approach and to show that the system can yield enough cells for clinical application. • The idea of generating pesudoislet by aggregating beta, alpha, delta cells using microwells (aim 4) for in vitro and in vivo functional evaluation has no preliminary data showing feasible protocols to generate the three different endocrine cells and in sufficient quantify to allow transplantation in mice. • There is one paragraph discussing translation of the 96-well plate using the TRAN 4 mechanism and of the 6-well plate and the microwell systems using the TRAN 1 mechanisms. But, without preliminary data on any of the prototypes, translation seem premature. • More quantitative data to support the IHC data shown in Fig. 7 and 9 would further support the rationale. • In Fig. 12 statistics is shown but bar graphs have no error bars.
No: 4	• The focus and goals of the proposed work from a biological and medical perspective seem unclear.
GWG Votes	Is the proposal well planned and designed?
Yes: 8	• The design of the research plan seems detailed. • The refinement of materials and device is well considered, the biological studies clearly designed, and a functional assay of cells in vivo will be undertaken.

No: 7	• The project plan and timeline is overambitious: It is recommended that the applicant focus on one endpoint with one or two aims and clear alternative strategies. A suggestion is focusing on the 96-well plate platform for screening optimal conditions to generate alpha, beta and delta cells. Generating preliminary data to support the applicability of the platform for dynamic modulation of substrate stiffness would enhance the significance of a high throughput approach to define culture parameters for differentiation of stem cells before implantation and for improvement in endocrine cell maturation would significantly advance the field. • Four aims to develop two different technologies for dynamic modulation of substrate stiffness for differentiation of stem cells into all three different endocrine cell types and microwells for aggregating them into pseudoislets make it unlikely there will be one prototype ready for translation. Applicants should focus on current aim 1 and one revised aim 2 for the translation of optimal culture conditions to allow applicability to large number of cells. • Milestones should be well formulated. The applicants need to distinguish between academic specific aims and product development milestones. The switch between a mechanical system to modulate stiffness in one device and the novel piezoelectric materials in another is disconcerting. Milestones should clearly focus on achieving necessary specifications for a tool that will be generally available and useful to stem cell biologists. • The application lacks specificity about criteria for successful deliverables. For example, it is unclear what types of protein modifications on the scaffold can be achieved, how they effect or do not effect stiffness properties. • A thorough discussion of potential pitfalls and alternative strategies is needed, especially since preliminary data on the specific technologies proposed are not available.
GWG Votes	Is the proposal feasible?
Yes: 10	• There is a good plan. • Excellent interdisciplinary team.
No: 5	• The team has all qualification and collaborations required but project is overambitious. • The project confounds focus on a specific biological system (pancreatic islet differentiation) versus optimization of a tool that can be produced in near-term for the community to utilize.

Application #	DISC2-11180
Title (as written by the applicant)	Development of Stem Cell Therapy for Sanfilippo B
Research Objective (as written by the applicant)	We propose to develop an autologous Neural Progenitor Cell transplantation for Sanfilippo B patient upon genetic correction.
Impact (as written by the applicant)	Sanfilippo B is a fatal inherited, lysosomal storage disorder (LSD), that affects children in early childhood. Currently, there is no therapy available for this catastrophic disease.
Major Proposed Activities (as written by the applicant)	• Genetic Correction of iPSC, to provide a functional copy of NAGLU. • Quantification of neuropathology, NAGLU enzymatic activity upon transplantation after 3 months. • Quantification of neuropathology, NAGLU enzymatic activity upon transplantation after 6 months. • Quantification of neurobehavioural defects upon transplantation after 6 months.
Statement of Benefit to California (as written by the applicant)	This application will contribute to 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	$899,999
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 75

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

Mean	73
Median	75
Standard Deviation	3
Highest	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 scientific 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	• Sanfillipo B syndrome (SBS; aka Mucopolysaccharidosis IIIB) is a severe lysosomal storage disorder for which treatments are lacking. This proposal offers a conceptually straightforward path to improving the treatment of individuals with this disease. • The autologous, gene-corrected approach could significantly help the quality of life of these patients.
No: 4	• The project is well-designed and provides some interesting possibilities for the long-term provision of a therapeutic enzyme but lacks detailed explanations for some experimental aspects. A more detailed explanation of the biochemical and neuropathological measures would have been important to include. Moreover, the behavioral tests selected were not necessarily the most appropriate.
GWG Votes	Is the rationale sound?
Yes: 8	• The cross correction idea with a neural cell type is sound. • The applicants aim to develop a stem cell-based therapy for SBS that would follow the initial enzyme replacement therapy (ERT) currently being used to prolong the availability of the missing enzyme. • The combinational aspect of the approach is novel and valuable.
No: 7	• The goal is to develop patient-derived neural progenitor cells (NPCs) for treatment of SBS. The idea is that such cells would be gene corrected followed by transplantation in order to provide enzyme replacement therapy. If it were successful, this would be an useful advance for this disease. Some data is provided to support the general concept, but there is a lack of discussion of the drawbacks that have been encountered in other similar diseases for which similar therapies have been studied (with Krabbe disease being a particularly strong example). • There is no indication as to why this approach would be better than the viral-based approaches that are being used for other lysosomal storage disorders, in order to express defective enzyme within the affected tissue (again, with studies on Krabbe disease being a particularly strong example). • It is not clear why this approach would be more effective then the macrophage-based approaches that already are in clinical trials for SBS, and no comparative studies are proposed.
GWG Votes	Is the proposal well planned and designed?
Yes: 3	• The applicants plan to employ CRISPR/Cas9 technology to avoid the inclusion of foreign DNA but provide preliminary data with GFP tags. The applicants need to clarify the position of the GFP tag and a rationale for the inclusion of this tag in their study. • A rationale for the assessment for gene and protein expression in the striatum should have been provided (Figure 7). • It is unclear what happens to the transplanted NSC cells, whether they migrate from their transplantation site, whether they differentiate. It is unclear why the cells are transplanted in the striatum and whether this is where the main pathology lies, and whether other cells of the brain not affected by this storage deficiency. All these points need further clarification.
No: 12	• Figure 4 shows that there are benefits to brain pathology in areas where the majority of transplanted NPC's successfully engrafted. Cells also appear to spread over a longer term and activities of hexosaminidase are significantly increased. • The amount of enzymatic correction that is reported seems impressive. • There is little consideration, however, of the problems of obtaining engraftment in the nervous system in the presence of inflammation, in the extent of tissue that needs to be engrafted, and the limitations to cell migration. The degree of engraftment in the immunodeficient mice is impressive, but the extent of inflammation existing in the immunocompetent organism may be considerably greater and represent a greater obstacle. • The animal model should include an intact immune system to demonstrate the utility of the autologous approach. • Viral gene augmentation approaches should be directly compared to the applicant's approach. • The site of implantation should be studied or justified better.
GWG Votes	Is the proposal feasible?
Yes:	• The project is well designed to achieve treatment outcomes in the mouse model of SBS.

10	• Whether this approach might scale to the much larger nervous system of the human is not a topic that is discussed. • In the context of developing a therapy to be studied in a preclinical mouse model, the project is well constructed. • It is positive in that they are proposing two different approaches to expressing a functional allele, but there is little discussion of the difficulties in providing NPC-based therapies for a global lysosomal disorder. • Transplantation is being conducted into newborn mice, and it would be of interesting to see discussion on what a reasonable transplant time in the human might be in order that the relevance of the transplant can be assessed. • Potential pitfalls and alternative experiments are adequately discussed for most of the milestones. However, a discussion of possible alternate strategies in the event that the humanized mice do not maintain the anticipated phenotype would have helped to strengthen this proposal.
No: 5	• The gene correction together with animal work is too ambitious for the 2 year timeline.

Application #	DISC2-11170
Title (as written by the applicant)	Oxygenated implant for insulin producing stem cells transplant to treat diabetes
Research Objective(as written by the applicant)	Subcutaneous implant containing insulin producing cells for type 1 diabetes treatment
Impact (as written by the applicant)	Lack of suitable donor islets, transplant rejection, and toxicity of drugs used for immunosuppression
Major Proposed Activities (as written by the applicant)	• Prove efficacy of stem-cell derived insulin-producing cells in the device using in vitro tests • Prove efficacy of stem-cell derived insulin-producing cells in the device to treat diabetic rats • Prove efficacy of stem-cell derived insulin-producing cells in the device to treat diabetic pigs
Statement of Benefit to California (as written by the applicant)	This research will develop a standard treatment of type 1 diabetes using an implant that contains stem-cell derived insulin producing cells. Such technology has the potential to eliminate the need for deceased donors for pancreas and islets for treatment of type 1 diabetes. In addition, this technology also has the potential to eliminate transplant rejection without the use of toxic drugs with harmful side effects.
Funds Requested	$978,488
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 70

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

Mean	72
Median	70
Standard Deviation	7
Highest	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 scientific 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 plan for a medical device that can allow transplanted beta cells to maintain oxygenation and perfusion after implantation. If successful, this device might be a good way to allow functional engraftment (although in a medical device requiring external ports) into type 1 diabetes sufferers.
	• A device to protect beta cells may allow transplanted cells to survive longer and allow better engraftment (as they already have a milieu).
	• The applicants propose a combination product for autoimmune diabetes that addresses:
	  ◦ cell sourcing using stem cell derived beta cells
	  ◦ immunoprotection for transplantation without immunosuppression, using immunoisolating devices for cell delivery
	  ◦ improving oxygen transport to encapsulated cells
	• Stem cell-derived beta cell delivery requires an encapsulation device for safety reasons to minimize risk of teratoma and retrievability and to prevent cell rejection. However, the device implanted with primary islets has not cured diabetes in clinical trials.
	• Glucose/insulin transport resulting in physiological blood glucose regulation by encapsulated cells is not addressed by oxygen supplementation and may be an issue in the poorly vascularized subcutaneous space.
	• There is no discussion about translation.

No: 6	*none*
GWG Votes	Is the rationale sound?
Yes: 7	• It is unclear how this device is going to be different from previous therapies. • The proposed research is based on a device already made, and also the grant shows that good pancreatic beta cells are also available. • There is some concern about how the insulin produced by transplanted beta cells can be expected to effectively integrate with the blood of the recipient. In addition, the transplanted cells need access to blood to sense glucose levels. • Even if the device has only access to sub-cutaneous glucose and not circulating blood, a delayed secretion of insulin would still be of immense use clinically in a number of patients.

No: 8	• The overall logic is clear, and there is some precedent for each step to achieve viable islet-like constructs isolated from immune attack and with sufficient oxygenation for survival and long term function.
	• Important components of the proposed study — oxygenation device and encapsulation system — have been tried before with somewhat disappointing outcomes. It is not clear that the proposed work advances the field sufficiently to overcome these bottlenecks.
	• The companies partnering for supplying beta cells and the device for providing the oxygen and immunoisolation increases the translatability of the approach. Preliminary data from both companies are convincing.
	  ◦ Impressive perifusion data of the stem cell-derived beta cells.
	  ◦ Device data in rats show complete protection but data in mini-pigs show rejection at postoperative day 70.
	• Preliminary data are poorly described and poorly presented.
	  ◦ A schematic of the device is missing.
	  ◦ In figure 4 and figure 5 there are black boxes covering the legend.
	• In vivo data using stem cell-derived beta cells show no diabetes reversal even when large numbers of cells were transplanted.
	• A major concern is risk of fibrosis development on the device which will compromise its long-term functionality.
	• In vivo data using stem cell-derived beta cells are not impressive despite the high number of cells used. It is unclear how many cells can be fit into the device, and whether it would that be enough to achieve diabetes reversal as expected outcome.
	• It is unclear whether the preliminary data provided were generated in the PI's lab or provided by the company, and whether feasibility of the proposed approaches have been evaluated in the PI's lab.
	• The implantation site may not be sensitive enough to fluctuating glucose levels.

GWG Votes	Is the proposal well planned and designed?
Yes:	• Milestones are not very clear.

7	• Clearly laid out development plan with quality components.
No: 8	• Testing in large animals of the combination product will increase clinical translatability. There is a plan to produce preclinical data in large animal models and collaboration with the industry for both device and cell source. • Testing should be done using human islets instead of rat islets to allow comparison with human stem cell-derived beta cells. • It is unclear whether it is feasible to culture primary islets and stem cell derived beta cells for three months in vitro; preliminary data showing survival for such a long time in vitro is needed. • The proposed 'n' in aim 2 is very small. It is unclear whether that would lead to statistically meaningful data. • In aim 3 they propose to compare clusters with small (<200µm) vs. large (>200µm) in diameter in diabetic pigs but in aim 1 and in aim 2 there is no plan to compare the two groups. It is unclear what the rationale is for the comparison, and for evaluating it in pigs only. • There is no mention on the device maximum capacity for islets or stem-cell derived beta cell clusters. It is unclear whether they would be able to fit enough cells to achieve a therapeutic efficacy, especially with stem cells that have reduced metabolic function compared to primary islets. • The grant is poorly written and data presented lack experimental details. • The details of the experimental plan seems to be quite cursory. • Foreign body reaction not described and may be an issue.
GWG Votes	Is the proposal feasible?
Yes: 9	• This grant contains a good plan to take the device from rodents to mini-pig tests which will position the device for human trials at the completion of the proposed work, if successful. • Highly experienced PI and team. Good collaboration with companies for sourcing pluripotent stem cells and for the oxygenation system. • Concern that the device collaboration is not spelled out more clearly — including a question of whether this major pharma company has a proprietary interest in the product that will benefit from a CIRM grant.
No: 6	• A great team combining academic with industry partners but the feasibility of the combined approach in the PI's lab hasn't been shown. • The panel had significant reservations about the ability of any implantable device to offer a realistic therapy. A 30 year history of implantable devices has shown that most if not all devices are ultimately fibrous or suffer from other problems so that any initial utility eventually fades. An exceptional argument and justification with careful referencing and contrasting to existing literature would be needed to persuade the panel.

Application #	DISC2-11176
Title (as written by the applicant)	Promoting myelin repair in Multiple Sclerosis via N-acetylglucosamine induced oligodendrocyte differentiation from neural stem/progenitor cells.
Research Objective (as written by the applicant)	Evaluate the ability of the simple sugar and dietary supplement N-acetylglucosamine in promoting myelin repair from endogenous stem cells.
Impact as written by the applicant)	Progressive neurodegeneration in multiple sclerosis (MS) lacks safe effective therapies. N-acetylglucosamine may stimulate endogenous stem cells to promote myelin repair and treat progressive MS.
Major Proposed Activities (as written by the applicant)	• Evaluate the ability of N-acetylglucoasmine in promoting human stem cells to differentiate into myelin forming cells. • Evaluate the ability of N-acetylglucoasmine in promoting myelin repair in mouse models of Multiple Sclerosis.
Statement of Benefit to California (as written by the applicant)	There is a great need for effective and safe treatments of progressive Multiple Sclerosis. N-acetylglucosamine is currently in an early stage clinical trial in MS to assess a role in inflammation. Positive results from the proposed new studies would re-direct a future Phase 2 clinical trial of N-acetylglucosamine to assess myelin repair and progressive MS. Such a trial would be based in California and success would provide a novel and safe therapy for Californians suffering from MS.
Funds Requested	$1,123,282
GWG Recommendation	(1-84): Not recommended for funding

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	7
Highest	84
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 scientific 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	• A dietary supplement (nutraceutical), if effective, is far more promising for research than other compounds as the path to translation is direct and immediate. • The therapeutic is safe and cheap - even if has only a minor effect, it is still a cost effective therapy. • It is hard to get substantial funding from the private sector for such research. • There are several advantages to nutraceutical therapies and the one presented here has a strong clinical basis.
No: 6	• The clarification regarding the ongoing trial versus the proposed activity is appreciated. The proposed study looks at potential remyelinating activity versus immunomodulatory activity of the dietary supplement. A future Phase 2 trial would be designed to assess different endpoints if the proposed study revealed that the compound effects remyelination. • The candidate is already in trial and in use for this condition (despite the applicants' statement many MS patient forums report usage of the compound). Compound is currently available for off-label use in MS without prescription and has low toxicity. If the study were proposing to study mechanism to develop second generation therapeutics, the application would be stronger, especially given issues with relatively low potency of the compound for effects on oligodendrogenesis. • The candidate is already "discovered" and under trial for this condition. Information on remyelination would could provide more impetus for its therapeutic use, and it would alter design of the proposed Phase 2 trial. However, it is unclear whether the study would actually alter use of the compound.
GWG Votes	Is the rationale sound?
Yes: 6	• Many of the comments from previous review are well-addressed. • The project would benefit from an actual survey or other evidence of how many MS patients currently use the compound. Perhaps a formal survey of doctors or other method of getting this information (e.g., polls on patient forums). It is unclear what the worldwide nutraceutical sales are. The sales are likely less than $1 billion, but it is not clear they are more than $100,000. • There are two separate rationales proffered: remyelination and immune modulation. The proposal might be stronger is only one rationale was used as primary hypothesis, and if preliminary data could support that rationale. This would simplify the experimental design. • There are still concerns regarding pharmacokinetics. It is unclear whether the 80mM concentrations required to enhance oligodendrogenesis be attained in vivo. Direct evidence to support this is not shown. Figure 3c shows serum levels approaching one micromolar, 5a shows effects in vitro at 60-80 millimolar. Figure 7 looks at developmental effects and is not informative for the adult brain. In fact most preliminary results are in developmental systems, not adult animals. Figure 8 is unconvincing.
No: 9	• Discrepancies in the preliminary data are concerning. • Insufficient preliminary data. • This nutraceutical compound has already been shown to have immune-modulatory capacities. It is therefore difficult to determine what the relevance is on re-myelination. Even if this was the case, the outcome would be the same. This is a significant issue with the grant given that the argument relies largely on the fact that the applicants claim a new mechanism for the compound.
GWG Votes	Is the proposal well planned and designed?
Yes: 3	*none*
No: 12	• Use of immortalized neural progenitors in Aim 1 not justified. It is not clear whether the project should be focused on neural stem cells, which are a developmental cell type, or adult oligodendrocyte progenitor populations. One part of study uses adult oligodendrocyte progenitor cells, but these cells cannot be expanded and it is therefore not clear how good a model they really are. • For milestones 1-3, there is a dependence on the ability to generate true human oligodendrocytes in vitro. This has proven very difficult from human ESCs and iPSCs, and there is no data provided demonstrating the ability to generate GalC+ or MBP+ cells. If they can't generate true oligodendrocytes in vitro, then milestones 1-3 are problematic.

	• In terms of in vivo studies, the indications that this treatment is immunosuppressive means that there is a confounding contribution to effects on myelination that will make interpretation of outcomes more difficult. • The planned mouse model development will be high risk and will likely be time consuming given the need to fully characterize the model once developed. However, the model is highly relevant and will add substantially to the planned work. • The mouse experiments may be over ambitious - creating a new model may be too difficult in the time frame. • The studies conducted with Cuprizone in adult mice suggest that there is a significant increase in myelin basic protein (MBP) and a reduction in degrading MBP. However, no data is provided to show that there is indeed an amelioration in myelinated axons, though the authors do add that they intend to address this point in future studies. • A simple Phase II clinical trial testing patient reported outcome measures would potentially help to justify these experiments. Something to show there was a hint of promise before spending millions on molecular experiments and endpoint measurements.
GWG Votes	Is the proposal feasible?
Yes: 7	• At least some the aims are feasible, and would at least shed light on the biology of the disease. • Applicants have provided data from their phase I study showing positive outcomes. The applicants report that there have been no adverse effects of the compound. • Though each milestone has a section dedicated to potential pitfalls, actual pitfalls are not clearly outlined nor alternative experiments suggested.
No: 8	• The PI is an expert in this area, as are the co-investigators.

Application #	DISC2-11069
Title (as written by the applicant)	A new platform for discovery: deriving hPSC-derived spinal sensory interneurons (INs) and developing tracking methods to treat injured or diseased spinal cords
Research Objective (as written by the applicant)	Produce a new tool - hPSC-derived spinal INs - and develop the methods to track them, thereby permitting paralyzed patients to recover the ability to sense their environment.
Impact (as written by the applicant)	We will derive new classes of hPSC-derived spinal neurons - authentic, distinct populations of sensory INs - that can be tracked in living animals
Major Proposed Activities (as written by the applicant)	• Genetic characterization of hPSC-derived spinal sensory INs • Track integration of hPSC-derived spinal sensory INs and motor neurons (MNs) in humanized mouse spinal cords • Improved directed differentiation protocols for hPSC-derived spinal sensory INs
Statement of Benefit to California (as written by the applicant)	Millions of Californians live with damaged or diseased spinal cords. These conditions are debilitating, affecting a patient's ability to move and feel. They are also expensive: the lifetime cost for a patient with spinal paralysis is estimated at $3 million. Our studies directing stem cells towards the neurons that permit us to sense the environment are an important step towards reversing spinal injuries. They will thus improve the productivity and quality of life of many Californians.
Funds Requested	$778,440
GWG Recommendation	(1-84): Not recommended for funding

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?

Yes: 11	• The project proposes a new approach to spinal cord injury-generation of spinal interneurons. The production of reporters for spinal interneurons would be useful for improving this approach for the treatment of spinal cord injury.. • The improvements to signaling strategies for differentiation are helpful.
No: 4	• Though the proposal has potential to be translated into a successful therapy for spinal cord injuries or diseases impacting the spinal cord, the applicants do not necessarily discuss how they envision the translation of their protocols and imaging technology in a clinical setting to benefit patients.
GWG Votes	Is the rationale sound?
Yes: 13	• The preliminary data is convincing but limited to the genesis of the relevant cell types. • The differentiation studies are very strong. However, issues remain with fidelity of in vitro cells to those in vivo, efficiency and scale-up to clinically relevant numbers. • This is a valuable idea but the major concern on this grant is the lack of functional studies/experiments. The design needs to incorporate a better assessment of cell integration such as electrophysiology and behavioural measures on a more significant "n" of animals.
No: 2	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 3	• No electrophysiology experiments are proposed.
No: 12	• The proposal is lacking assessment of functional integration of transplanted cells which is key to determine the outcome. The investigators could include electrophysiological assessment of functional integration into damaged circuits. • There are concerns over the efficiency of the production of the desired cell types that suggest potential long delays towards therapy. • Applicants present a nice strategy for tracking neurons in vivo and a good plan for mapping gene expression in bonafide spinal interneurons long-term. However, some data may not be available within the time frame of the grant. • Despite using both iPSCs and ESCs, the applicants state that hESCs are difficult to obtain and hence present a major concern. It is unclear why they are not using only iPSCs since the applicants already intended to compare their iPSCs to the different cellular populations normally seen in the spinal cord. A more thorough explanation for using both cell types is needed.
GWG Votes	Is the proposal feasible?
Yes: 12	• Excellent team. The PI is an outstanding neuroscientist, and the collaborator provides expertise in imaging. • The team could use more translational expertise in spinal cord injury. • The applicants do not discuss pitfalls and possible setbacks, hence it is difficult to assess feasibility.
No: 3	• Assays of function seem to be lacking, reducing feasibility in terms of the ultimate goal of a medically relevant outcome.

Application #	DISC2-11089
Title (as written by the applicant)	BCN057; a novel small molecule for mucositis/oral mucositis
Research Objective (as written by the applicant)	A small molecule drug that promotes stem cell survival within epithelium in the context of chemo/radiation but does not protect tumor tissue leading to the mitigation of oral mucositis.
Impact (as written by the applicant)	There are no drugs to prevent oral mucositis and as supportive care after chemo/radiation we hope to introduce supportive care for epithelium after chemo/radiation.
Major Proposed Activities (as written by the applicant)	• Ex-vivo human oral organoid studies with our drug to examine tissue response in the context of chemo and radiation. We will measure preservation of function and stem cells. • Determine the effect of our drug with radiation/chemo induced oral mucositis in a murine model of HPV+/- head and neck tumor. • In vivo studies with our drug and oral mucositis in healthy rodents using both chemotherapy and radiation treatment in a clinically relevant setting.
Statement of Benefit to California (as written by the applicant)	Our major discovery are small molecule drugs which preserve stem cells in the case of radiation and chemotherapy and at the same time, show that the depletion of these cell populations in normal tissue from clinical therapy or other have debilitating effects on the health of patients. If realized, this will be a paradigm shift in the drug industry could expand new products onto the market from the pharma industry which is highly represented in California. Revenue and employment are impacts.
Funds Requested	$896,794
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 67

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

Mean	67
Median	67
Standard Deviation	3
Highest	75
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 scientific 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	• Protection of normal tissue stem cells from chemotherapy or radiation-induced damage constitutes a stem cell technology that would significantly improve patient care. Application in oral mucositis addresses a significant unmet need that would improve patient care. • The proposal focuses on an interesting problem.
No: 6	*none*
GWG Votes	Is the rationale sound?
Yes: 6	*none*
No: 9	• There is very little information on the molecular mechanism of the compound. The proposal would benefit form a more detailed description of the initial screen and the phenotypes used. A standard approach would be to perform some target identification first. The proposed experiments are very descriptive. • Most of the preliminary data are presented from models with intestinal stem cells. The data provide compelling evidence for protection of tissue from damage by radiation and chemotherapeutic agents. The data support the proposed project, with the caveat that there is no guarantee the oral stem cells will behave equivalently. • A human ex vivo model for oral epithelium/mucositis is not yet established. There are concerns about using tongue cells exclusively for this model.
GWG Votes	Is the proposal well planned and designed?
Yes: 6	• The proposed experiments are well-designed.
No: 9	• The project includes relevant in vitro and in vivo models and proposes to seek information on efficacy & dosing. • There is uncertainty about the development of a key human cell model. • Experiments to determine molecular mechanism by which candidate compound acts is not presented, which is likely to delay further development.
GWG Votes	Is the proposal feasible?
Yes: 8	• The proposed timelines and milestones are appropriate. • The project begins with an interesting lead compound already in hand. • There is uncertainty about the key efficacy model in human cells: (1) an appropriate model is not clearly defined, and it is unclear whether it can be achieved; (2) the nature of a crucial collaboration for the model is not defined clearly in the application.
No: 7	*none*

Application #	DISC2-11182
Title (as written by the applicant)	Assessment of Novel Depots of Adipose-Derived Stem Cells for Chronic Rotator Cuff Injury
Research Objective (as written by the applicant)	To show that fat-derived stem cells collected from around our muscles is a safe cell source for repairing chronic rotator cuff injuries that is better at regeneration than other common fat sources.
Impact (as written by the applicant)	Develop an adult stem cell-based intervention to be used in concert with surgical repair that will encourage muscle regeneration and prevent re-tearing of the rotator cuff.
Major Proposed Activities (as written by the applicant)	• Evaluate the equivalency of fat tissue and fat-derived stem cells from regions that surround the upper trunk muscles and from the abdomen in humans and rabbits. • Establish the degree of improved regenerative potential of stem cells derived from fat surrounding the rotator cuff muscles compared to abdominal fat. • Establish why fat from around our muscles is better at regeneration by assessing immune response, tracking stem cell location, and correlating position and amounts with tests of muscle function. • Consult with internal and external teams of scientists on project outcomes and conduct preliminary meeting with FDA to discuss establishing a clinical trial.
Statement of Benefit to California (as written by the applicant)	More than a half million Californians live with chronic rotator cuff tears. While there have been improvements in surgical repair methods, re-tear rates are as high as 50% in the decade following surgery. Degeneration of cuff muscles limit the success of surgical repair, so here we will use metabolically active fat from around rotator cuff muscles to develop an injectable cell population that regenerates muscle in conjunction with surgical repair, thus increasing patient quality of life.
Funds Requested	$1,305,770
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 65

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

Mean	67
Median	65
Standard Deviation	6
Highest	75
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 scientific 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	• Potential for strong impact in a large unmet medical need. • Stem cell based rotator cuff injury alleviation is of good impact. • It is unclear if rabbit data will allow for human trials. This was also an issue in the first submission. • There is a statement included in the resubmission section addressing previous comments along the lines that if the rabbit adipose-derived stem cells (ADSCs) do not work that well, the study will still lead to a clinical trial since even worse results have led to clinical trials.
No: 7	• Because the scientific premise is weak, it is difficult to assess the significance and impact of this project. • Human cells need to be tested.
GWG Votes	Is the rationale sound?
Yes: 3	• The rationale is sound although the muscle regenerative potential of ADSCs is still questionable. Nevertheless, the revised proposal explores both mechanisms (fusion vs. paracrine).
No: 12	• There are clear quantitative go/no go thresholds. • There is insufficient evidence of equivalency of rabbit vs human epimuscular ADSCs. • There is insufficient data to support the use of epimuscular ADSCs. • Evidence of myogenic differentiation is limited. • qPCR analysis in Fig 8b is unconvincing. Only three genes are examined, with only one noted as significantly different between beige and white/brown fat. An array-based assay must be done and/or many additional genes analyzed. These data suggest that the tissues are NOT similar. • It appears that GFP labeled rabbit cells will be used in the rescue experiments. It is unclear if team will be looking for GFP+ cells outside of the injection site.
GWG Votes	Is the proposal well planned and designed?
Yes: 3	• A strength is clear go/no go thresholds. • The milestones are well put together and appear achievable. • The analysis of the secretome will provide hits but it is not clear how they will be validated functionally.
No: 12	• There are some concerns about the utility and relevance of the stem cells to be used. • Supportive preliminary data is provided. A comparison between rabbit and human epimuscular ADSCs is shown, but only at the level of gene expression. In addition, as discussed above, preliminary data for the myogenic potential of these cells is not convincing. • $26K is budgeted in travel. It is unclear why the “executive management team” all need to attend a meeting to present results. • The budget is not appropriate. 100% for a senior graduate student will not allow the student to do any other work (which would include writing a thesis on projects on any other topic).
GWG Votes	Is the proposal feasible?
Yes: 8	• The applicant has a strong team with all the relevant resources, skills and expertise. • The milestones are logical and likely to be achieved with the proposed timeline. • It is possible that all proposed experiments can be accomplished during the two-year time frame.
No: 7	• There are some concerns whether the rabbit cells model human cells.

Application #	DISC2-11002
Title (as written by the applicant)	A generic drug-discovery tool through phenotypic assays mimicking the early human development.
Research Objective (as written by the applicant)	We create a generic tool for drug-discovery that can be applied to a wide variety of diseases, through the reconstitution of human embryonic development from embryonic stem cells.
Impact (as written by the applicant)	The pace of new drug availability for genetic diseases has been extremely low. Our tool will highly impact the efficiency of the process by which drugs in early stages of development reach the clinic.
Major Proposed Activities (as written by the applicant)	• Create a relevant siRNA library associated with known monogenic disorders. • Perform a siRNA screen of disease-associated genes for phenotypic modification of the neuruloids. • Develop three ready-to-screen platforms associated to three monogenic diseases. • Write a draft Target Product Profile
Statement of Benefit to California (as written by the applicant)	There are two main benefits for California: First, we will introduce a technology which does not yet exist outside the laboratory of the founders in a different state. This complements the mission of CIRM, while commercialization of our tool will also create new jobs for the CA work force. Second, our tool will allow for a faster and more efficient drug development to eventually benefit Californian citizens suffering from genetic diseases that currently cannot be effectively treated or cured.
Funds Requested	$500,000
GWG Recommendation	(1-84): Not recommended for funding

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	63
Median	65
Standard Deviation	9
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 scientific 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	• The power of stem cell approaches could be used in this case for monogenic disorders. • Increasing the capacity to screen compounds using in vitro assays could accelerate drug discovery. • Progression to translation has been discussed, but seems very optimistic. The proposed research is at a very preliminary stage, and may be risky.
No: 11	• The project will generate a screening tool but it is unclear how the path to translation will lead to clinical impact. • There is not enough focus for translational efforts. • It is unclear what the product will be.
GWG Votes	Is the rationale sound?
Yes: 5	• It is unclear whether the screen works. • Identifying diseases that have neuruloid in vitro phenotypes could then allow neuruloid phenotype to be used to screen compounds affecting that disease. However, it is not clear that any diseases would create a neuruloid phenotype, and if a particular gene for a particular disease is affected, it is not clear that altering that phenotype with a compound would also translate to altering the clinical course of the associated disease.
No: 10	• While the rationale is good in principle, it is unknown how often a robust phenotype will be observed for any given disease. • The use of deep learning computational analysis may well provide a sophisticated way to discern phenotypes that can be ascribed to a mutation, and may allow drug discovery by reversal of phenotype. However, it is unclear if such subtle in vitro phenotypes are relevant for in vivo aspects of disease pathology. • There is not a clear link between the in vitro neuruloid phenotype and disease. • The siRNA procedure for the positive control is unclear.
GWG Votes	Is the proposal well planned and designed?
Yes: 4	• Distance between cell model and real disease. • The screen design is excellent. A use of machine learning is a strength of the approach. • The use of multicellular morphogenesis as a screening tool has the potential to push the screening field forward.
No: 11	• The grant lacks important preliminary data. For instance, siRNA will be used to see which genes can give phenotypes in the neuruloid assay, and the number or diseases that can be addressed by this approach therefore unknown at present. It is unclear if "responsive" diseases will be relatively common or relatively rare, in which case the proposed method may not be broadly applicable. • The neuroloid preliminary data is quite impressive, but it is unclear how sensitive this assay will be across the 3500 or so proposed monogenic disorders to be assessed, and the approach may be too broad. • It will likely take more than two months to carefully comb through the genetic disorder catalog and create an siRNA library.
GWG Votes	Is the proposal feasible?
Yes: 9	• This is a high risk/high reward proposal but the project is likely to generate promising hits for further analysis. • It is feasible to execute all the protocols described, but it is unclear what the overall likelihood of success would be. • More preliminary data is needed. For example, taking a small number of disease/gene pairs - ideally one with several known drugs - and show that an siRNA neurulation model responds to that known drug. ie., show that this method can replicate/detect something that is already known using classical methods.
No: 6	• This work will yield a screening system for monogenic diseases, but it is unclear if the model is relevant for disease.

	● The milestones can be completed during the proposed funding period.

Application #	DISC2-11094
Title (as written by the applicant)	Modulating Lgr5+ crypt stem cells by RSPO1 for the treatment of colitis
Research Objective (as written by the applicant)	Our objective is to assess the therapeutic potential of locally administered RSPO1 as an activator of stem cells for the treatment of ulcerative colitis.
Impact (as written by the applicant)	Ulcerative colitis, inflammatory bowel disease
Major Proposed Activities (as written by the applicant)	• Developing an ulcerative colitis mouse model • Optimize RSPO1 activity in vitro and in vivo • Develop a scalable cell line process to produce RSPO1 • Therapeutic activity of RSPO1 in ulcerative colitis model
Statement of Benefit to California (as written by the applicant)	Inflammatory bowel disease causes significant morbidity in California, and successful efforts to treat this condition will confer an important benefit to the citizens of California.
Funds Requested	$1,384,700
GWG Recommendation	(1-84): Not recommended for funding

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	63
Median	65
Standard Deviation	4
Highest	70
Lowest	55
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 scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 12	• The investigation of RSPO1 as a potential therapeutic for inflammatory bowel disease (IBD) has the potential for significant medical impact given lack of effectiveness and/or side-effects associated with current treatments.

	• The project addresses several translational aspects, including dosing, delivery, and manufacturing. • The path from testing in a murine model to translation in humans is not described.
No: 3	• The proposal is a great opportunity to target IBD. • The RPSO1 protein may lack sufficient bioavailability or potency. Long-term treatment may be required, and the underlying immune dysfunction and pathogenesis is not addressed.
GWG Votes	Is the rationale sound?
Yes: 5	• Wnt activation has been shown to work well with endogenous stem cells. • There is a significant body of work showing that Wnt regulates crypt stem cells. Thus, a sounds mechanistic basis underlies the project.
No: 10	• There are major concerns about the models used in the proposal. • There are some concerns about the validity of the chemically-induced damage model as well as the organoid model. • There is strong evidence for RSPO activity in control of normal intestinal proliferation. However, evidence is needed to demonstrate that insufficient Wnt signaling is responsible for pathological features of human IBD or that failure of intestinal regeneration is a limiting factor in disease.
GWG Votes	Is the proposal well planned and designed?
Yes: 0	*none*
No: 15	• Investigations do not focus strongly on disease but rather on the effects of RSPO1 on normal intestine and in an acute damage model. The model is not adequately justified as predictive of results in inflammatory bowel disease, as it is acute and chemically induced. • The acute model may not be a suitable model for a chronic disease. • The intestinal organoid experiments are not well-integrated into the study. • The study lacks controls comparing systemic delivery with enema delivery. Likewise, comparison to current gold standard treatment is missing.
GWG Votes	Is the proposal feasible?
Yes: 6	• Milestones and success criteria are appropriate. • There are concerns over whether results with RPSO1 in acute damage model will translate to a clinical situation.
No: 9	• Preliminary data is needed to show that the enema delivery method will work.

Application #	DISC2-11202
Title (as written by the applicant)	Strengthening hematopoietic stem cell self-renewal program to improve transplantation
Research Objective (as written by the applicant)	We will improve the function of cultured blood stem cells using a novel blood stem cell regulatory factor
Impact (as written by the applicant)	The proposed studies will make blood stem cells more available for the treatment of blood diseases
Major Proposed Activities (as written by the applicant)	• To optimize a method for providing new HSC regulatory factor in cultured human blood stem cells to improve transplantation • To evaluate if the novel HSC regulatory factor can be used also in adult bone marrow and mobilized peripheral blood stem cells • To determine if inducing novel HSC regulatory factor in blood stem cells generated in culture improves their function • To determine the timing and cell type when the novel HSC regulatory factor is induced during development • To test candidate factors that can induce the novel HSC regulatory factor • To screen for potential factors that can induce the novel HSC regulatory factor
Statement of Benefit to California (as written by the applicant)	This work will improve the treatment of patients who require blood stem cell transplantation for the treatment of blood cancers or inherited blood diseases.
Funds Requested	$1,404,000
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: --

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

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

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific 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 proposal addresses an unmet need. • It is not clear the project could be moved to a translational product in two years.
No: 7	• The project is basic science focused and translational impact is unlikely. • Overall, a very preliminary stage grant. A detailed analysis of a novel factor critical for self-renewal is too early for clinical applications. • It is hard to know at this stage of discovery but the problem is a big one and needs to be solved.
GWG Votes	Is the rationale sound?
Yes: 5	*none*
No: 9	• Because the preliminary data were limited the rationale is a concern. • The limited preliminary data detracts from the proposal. • The protein knockout mice are viable. • The relationship between engraftment and self-renewal is not established, and thus it is unlikely the protein will have this effect in hPSCs. • An increase in self-renewal capacity is important for a cell therapy; it is not clear that expansion only is enough. • The aims are too diffuse and need focus. • The plan is solid otherwise.
GWG Votes	Is the proposal well planned and designed?
Yes: 4	• There is a strong basis in biology, but the proposal is observational and exploratory in nature. • A very detailed study and molecular characterization.
No: 10	• There are so many little experiments that it was hard for the applicant to address them all carefully with regards to adverse outcomes, alternatives etc... • The protein has been knocked out in mice and does not alter hematopoiesis, which is a concern. • The proposal is not focused on achieving a single candidate in the available time frame.
GWG Votes	Is the proposal feasible?
Yes: 4	• The investigator can carry out many of the experiments based on the fact that they are standard and have been achieved with other molecules before.
No: 10	• There is no evidence that the molecule will have these potential effects and move to the clinic. • The project is very preliminary; the paper is still to be published. • There is no evidence a small molecule could disrupt the current manner in which the protein is believed to work. Screening will likely be unsuccessful. • It will be very hard to identify small molecules for this protein. • A small molecule screen appears unlikely to be fruitful at the level needed to get a candidate in the time frame of the proposal.

Application #	DISC2-11141
Title (as written by the applicant)	Embryonic Stem Cells for Corneal Endothelial Dysfunction
Research Objective (as written by the applicant)	We propose to develop a stem cell-derived corneal endothelial cell useful in the treatment of corneal edema.
Impact (as written by the applicant)	The cell product will be used to treat corneal edema after trauma, after cataract surgery (e.g. pseudophakic bullous keratopathy), or in disease (e.g. Fuch's dystrophy).
Major Proposed Activities (as written by the applicant)	• Optimize the cell product using morphological and functional assays in vitro. • Optimize the magnet nanoparticle technology for cell delivery. • Validate the cell product in vivo using rodent and rabbit models to test safety and efficacy. • Prepare and submit a data package to the FDA for a pre-IND meeting anticipating move to human testing.
Statement of Benefit to California (as written by the applicant)	6% of Californians report low vision and a sizable fraction of these are due to corneal edema. The development of this cell product will be useful to treat Californians, and the development in California will support job growth within the state.
Funds Requested	$1,412,156
GWG Recommendation	(1-84): Not recommended for funding

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 scientific 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 approach is novel and, if successful, could develop a stem-cell based therapy would be a significant improvement to current therapy.

	• Alternative strategies for corneal transplantation would be excellent, but there are concerns about the ability of the approach to succeed based on analysis of the preliminary data.
No: 8	• Although alternative strategies for corneal transplantation would be highly impactful, it is unclear whether the approach would be successful based on the preliminary data.
GWG Votes	Is the rationale sound?
Yes: 2	*none*
No: 13	• The project is based on a sound scientific rationale in that, the use of magnetic particles to attract hESC-CECs to repopulate the endothelial layer in corneal edema is both logical and highly innovative. • The preliminary data do not support a significant effect of the hESC derived corneal endothelial cells in corneal regeneration. • Preliminary data seems incomplete and lacking in detail. For instance, in Fig. 9, there seems to be no difference in corneal thickness that is statistically signifiant between cell-treated versus vehicle only controls. In addition, the data for corneal clarity is qualitative rather than quantitative, leaving the therapeutic effect unclear. • There are some concerns about the level of characterization of the corneal cells produced by differentiation.
GWG Votes	Is the proposal well planned and designed?
Yes: 0	*none*
No: 15	• The project plan assumes success, though key proof-of-concept data to show the approach really works is needed. • There are concerns about whether the study design will meet the goals of each milestone. • The in vitro potency assays are not clearly linked to efficacy in vivo. • More studies on hESC-CEC are needed as Figure 3c only describes hCEC. • The rabbit model may not be the best model as the rabbit is an aggressive wound healing model and is not comparative to human disease. • Fresh human globes with endothelial deficiency are readily available from eye banks across the US and use of these would greatly enhance the translational potential of these studies. • There are safety concerns around what happens to the unattached cells in the aqueous cavity. This will be a major safety concern when seeking FDA approval. The applicant does not indicate what % of these cells attach to Descemet's membrane and those in the aqueous. There is not sufficient consideration to identifying where these cells are relocating in the vitreous cavity; there are many ways to identify them in the rabbit model since these are human cells.
GWG Votes	Is the proposal feasible?
Yes: 3	• The milestones appear achievable. • There is some concern that the research plan is not sufficiently designed around manufacturing and delivery considerations in Milestones 1 and 2. • The milestones and anticipated project outcomes are likely to be achieved within the proposed timelines.
No: 12	• Though the timelines and milestones are logical and reasonable, there are concerns about the quality of the preliminary data.

Application #	DISC2-11018
Title (as written by the applicant)	Development of USP16 inhibitors as therapy for Down's syndrome and/or age-related diseases.
Research Objective (as written by the applicant)	The object of this research is to develop selective USP16 inhibitors as therapy for age-related neurodegenerative diseases.
Impact (as written by the applicant)	This would be the first therapeutic agent to prevent or alleviate somatic stem cell age-related pathologies.
Major Proposed Activities (as written by the applicant)	• To develop a small molecule inhibitor against USP16. • To test the inhibitor's efficacy in rescuing stem cell defects seen in Down's syndrome. • To test the inhibitor's efficacy in rescuing neuro stem cell defects seen in Alzheimer's disease. • To test the inhibitor's efficacy in rescuing mesenchymal stem cell defects that contribute to osteoporosis and glucose intolerance.
Statement of Benefit to California (as written by the applicant)	The goal of the proposed research is to generate a small molecule inhibitor against USP16. The development of this inhibitor can potentially be used as therapy to alleviate and/or prevent the pathologies associated with Down's syndrome, Alzheimer's disease, osteoporosis or type 2 diabetes mellitus. This clearly would provide great benefits to the people of California by minimizing the suffering of the patients while also decreasing the costs associated with the care and treatments.
Funds Requested	$1,413,129
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: --

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

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

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 5	• This application may lead to therapies for Down's Syndrome (DS) and diseases of aging by inhibiting USP16, whose gene is present in 3 copies in DS. • The investigators have identified molecules that may regulate stem cell senescence and self-renewal. These findings are very exciting but an important concern is whether a single gene accounts for the varying phenotypes seen in DS, or for the subset of aging phenotypes. Trisomy, for example, has also been linked to increased incidence of Alzheimer's disease in DS.
No: 9	• The project will potentially identify an inhibitor of USP16. • The goal of the proposal is unclear.
GWG Votes	Is the rationale sound?
Yes: 1	• The proposed USP16 inhibitors, if developed, would be expected to have an impact on adult stem cell behavior in vivo, but the proof of concept data needs further development.
No: 13	• A much more detailed research plan is needed. • Studies performed in a mice knockout or conditional knockout for USP16 or using shRNA to show that removal of USP16 is useful to treat DS would provide evidence for the role of USP16 in DS. • The applicants state that the increase in inflammation seen selectively at older ages is related to accelerating aging, however, they do not show the presence of this phenotype in older AD mice nor do they comment on the possibility of inflammation driven by the presence of aggregated proteins. • Applicants comment that the change in stem cell differentiation and inflammation is not specific but data is provided for only two mutations. • When validating stem cell deficits in the animal model, it is not clear why they used a marker of astrocytes instead of nestin to demonstrate that there is increased differentiation. The astrocyte marker can be increased by inflammation, making interpretation of this data is difficult. • It is not discussed why the animal models have increased stem cell differentiation while the cellular models display decreased differentiation. • The molecule may alter stem cell populations in vivo, but that is not proposed to be tested. The only tests are using differentiated cell lines.
GWG Votes	Is the proposal well planned and designed?
Yes: 1	*none*
No: 13	• There is some concern about the focus on USP16, which is one of dozens if not hundreds of genes in trisomy 21. It is unclear if USP16 is the primary cause of the disorder. • It is unclear why so many molecules are being tested or how the fluorescent enzymatic assay works. • A plan for in vivo validation is not presented. Mouse experiments are proposed in milestone 2, but no experiments are included in the proposal. • Milestone three is not described in much detail in the proposal.
GWG Votes	Is the proposal feasible?
Yes: 1	• The proposed research would have the effect of identifying candidate compounds that might impact stem cell function in vivo.
No: 13	• The project is designed to identify a USP16 inhibitor with an aim to curb early aging in DS. However, pitfalls or alternatives are not discussed. • The team can perform the proposed experiments. • The screen is poorly described.

Application #	DISC2-11010
Title (as written by the applicant)	Developing a therapy to abrogate fibrosis-initiating progenitor cells in progressive organ fibrosis
Research Objective (as written by the applicant)	We will develop a therapy to remove the stem cells that cause scarring diseases throughout the body and in this way stop progressive scarring of organs
Impact (as written by the applicant)	Progressive organ scarring diseases are responsible for 45% of deaths in the United States. By stopping ongoing scarring or even potentially reversing scarring, we can potentially save many lives.
Major Proposed Activities (as written by the applicant)	• We identified a hit compound from a drug screen that stops scarring by removing the stem cells that cause scarring. We will improve this compound to make it a drug that can move forward to the clinic. • We will show that the improved drug works well in human tissues from organs with scarring • We will show that the improved drug works well in clinically relevant models of scarring diseases • We will demonstrate that the improved drug is generally safe and not toxic to human tissue. • We will identify secreted biomarkers that predict response to this drug by removing the fibrosis inducing stem cells.
Statement of Benefit to California (as written by the applicant)	This research will benefit California in several ways. First, this research provides fundamental new knowledge regarding progressive organ fibrosis from stem cells for the field. Second, our discoveries will ultimately increase the fibrosis cure rate, thereby reducing medical costs, and improving the health of Californians. Third, our discoveries will provide the basis for licensure to pharmaceutical companies in California or raise investment from venture capitalists to benefit California.
Funds Requested	$1,292,000
GWG Recommendation	(1-84): Not recommended for funding

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 scientific 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	• Alleviating organ fibrosis is an unmet medical need. • Fibrosis is a major medical problem associated with many different pathologies. If the project is successful, it could lead to the development of a more effective anti-fibrotic drug. • A drug that prevents/slows fibroblast-initiating mesenchymal progenitor (FIP)-dependent fibrosis would address current clinical limitations in the treatment of fibrotic conditions.
No: 7	• This is an interesting proposal that could produce novel anti-fibrotic agents. However, the validity and identify of the FIPs is not clear and needs further exploration/validation. It is also unclear how FIPs are specifically generated from iPSCs.
GWG Votes	Is the rationale sound?
Yes: 3	• The rationale is sound based on preliminary results, but the application would be stronger if the PI had published these initial in vitro and in vivo results with the small molecule. • Strong preliminary data.
No: 12	• The evidence for FIPs is limited. • If the FIP concept is validated as well as validation of generation of FIPs from iPSCs, their use for drug screening would be a valuable tool.
GWG Votes	Is the proposal well planned and designed?
Yes: 0	*none*
No: 15	• The milestones are a concern. Milestone 1 proposes to synthesize 3-4 analogs every 6 weeks for a total of 60 analogs for up to 21 months, almost the whole length of the study. Milestone 2 proposes to investigate leads from milestone 1 to further identify the most promising analogs over the same time period: month 4 to 21. • The justification for the eye models is unclear as there are many other in vivo models available. The commercially available eye test is a measure of eye irritation and the clinical scoring is not a measure of fibrosis. The MTT endpoint is a measure of cellular respiration which does not necessarily reflect cell death. In addition, this is an epithelial screen and does not assess what effect the candidates may have on corneal or conjunctival fibroblasts. • Careful examination of Fig 8d is concerning since the one image is a higher magnification and a different ocular location compared to the two adjacent panels. • The justification for the biomarker aim (5) and how it would help with drug design or clinical diagnosis is unclear.
GWG Votes	Is the proposal feasible?
Yes: 2	*none*
No: 13	• While there is some very interesting preliminary data, the proposal is overambitious for a 2-year period particularly as each aim is dependent on the preceding aim. The potential problem/alternative approaches sections don't address well what will be done if the experiments don't work. • There is a strong likelihood that the milestones will not be achieved within the proposed timeline. The investigators are developing analogs out to the third quarter of the second year which will give them insufficient time to test them in their ex vivo and in vivo models. The biomarker profile timeline has similar concerns. • More substantial involvement from a chemist is required for this project to be successful. It appears that the consultant will contribute only 20 hours per year to this study and no letter of support is provided. It is not clear how the consultant will interact with the investigators or the company that will be contracted to make the compounds.

	• Since a major feature of the proposal is testing the candidates in eye models adding an expert in this field would be a benefit. • It is not clear who will hold the IP on any compounds generated.

Application #	DISC2-11019
Title (as written by the applicant)	Development of a novel therapeutic for Alzheimer's Disease targeting aberrant microglia function
Research Objective (as written by the applicant)	A therapeutic candidate antibody will be generated and chosen based on its ability to ameliorate microglia dysfunction in assays using iPSC-derived microglia with Alzheimer's Disease-linked mutations.
Impact (as written by the applicant)	The therapeutic we generate will be used to treat Alzheimer's Disease, a disease that currently lacks a cure, by targeting microglia as an underlying cause of disease initiation and progression.
Major Proposed Activities (as written by the applicant)	• Differentiate iPSCs engineered with knockout or overexpression of MS4A family genes and patient-derived iPSCs into microglia • Implement quantitative assays to characterize microglia state/function and identify aberrant behavior in iPSC-microglia with disease-relevant mutations • Generate brain-penetrant antibodies against MS4A family target(s) identified to contribute to microglia dysfunction • Scale up functional microglia screening assays and apply antibodies to identify specific antibodies with desired functional effect • Apply curated list of target antibodies to sophisticated, disease-relevant functional screening assays using co-cultures and stressors to model the aging/diseased brain • Identify large molecule therapeutic candidate and prepare to enter translational stage activities
Statement of Benefit to California (as written by the applicant)	The therapeutic candidate we identify will be used to treat Alzheimer's Disease, a progressive neurodegenerative condition with no therapy that is able to slow the course of cognitive decline. AD represents the fifth-leading cause of death in California and affects 10% of people 65 and older. As the people of California age, increasing numbers will be at risk for AD, and providing care for these individuals will come at a significant cost to our healthcare system and to the families afflicted.
Funds Requested	$1,214,650
GWG Recommendation	(1-84): Not recommended for funding

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 scientific 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: 10	• This proposal aims to target two surface receptors, which are primarily expressed on microglia and have been shown to have strong genetic links to AD. This will be done by using iPSC differentiated into aberrant microglia to test antibody-based therapy (peptide vaccine). This could be an interesting approach but more data is needed to support it. • Preliminary data does show that antibodies are able to decrease mRNA expression of some inflammatory cytokines in iPSC-derived microglia to decrease human macrophage migration in vitro and to enhance myelin phagocytosis in short-term assays in vitro.
GWG Votes	Is the rationale sound?
Yes: 1	*none*
No: 14	• The rationale for this proposal is not well supported. Identification of disease-relevant phenotypic changes in the microglia, generation of antibodies that restore normal function in the microglia, and generation of brain-penetrant therapeutic antibodies has not been accomplished. • More substantial data is needed to support this application. The cell model has not been fully characterized and there is no evidence that the antibodies, which have yet to be identified, will cross the blood brain barrier or target the as of yet undefined deficits in microglia caused by these mutations. • There needs to be a stronger rationale for choosing to target microglia and these two specific receptors. Table 1 which shows that they are not the most strongly expressed in microglia, and Figure 2 which demonstrates that one receptor is the family member least effected by environmental changes and there is no data regarding the second receptor.
GWG Votes	Is the proposal well planned and designed?
Yes: 0	*none*
No: 15	• The premise is largely theoretical with very little supportive preliminary data. • They hope to be able to model aging-type changes that might prove relevant to understanding Alzheimer's disease, but it is not clear they can do this. • There is no data on any phenotypes of relevant to Alzheimer's disease, or of any phenotypic changes caused by knockout or overexpression of the proposed proteins. • There also is no data presented indicating that they can generate antibodies that would have the necessary ability to enter and distribute in the central nervous system.
GWG Votes	Is the proposal feasible?
Yes: 0	*none*
No: 15	• The approach is singularly focused, and alternatives are not articulated. At the same time, there are multiple opportunities for failure. • This proposal is too ambitious to be completed within the two-year timeframe proposed. For example, the investigators have assigned a period of six months to humanize the chosen antibody, develop a specialized mouse line to test their antibodies in and to conduct pharmacokinetics and target engagement studies.

Application #	DISC2-11068
Title (as written by the applicant)	IPSC-derived Endothelial cells for Treating Peripheral Vascular Disease
Research Objective (as written by the applicant)	Endothelial cells and their progenitor cells will be derived from human induced pluripotent stem cells to reconstitute vasculature and restore blood perfusion in ischemic tissues.
Impact (as written by the applicant)	Critical limb ischemia represents a significant unmet medical need without effective medical therapies for patients at high risk of amputation, and it may be alleviated by hiPSC-based cell therapy.
Major Proposed Activities (as written by the applicant)	• Determine if an integrin avb3 ligand peptide, LXW7, provides pro-survival and functional benefit for hiPSC-ECs under low serum and hypoxia in vitro. • Enhance engraftment and functionality of hiPSC-ECs in ischemic mouse limbs using LXW7-modified collagen hydrogel. • Optimize dose and time of cell administration to promote robust angiogenesis/vasculogenesis and improve perfusion therapeutically in the hind limb ischemia (HLI) mouse model. • Enhance the therapeutic effect of hiPSC-ECs in the HLI mouse model by co-transplantation of hiPSC-ECs and their progenitor cells.
Statement of Benefit to California (as written by the applicant)	Critical limb ischemia (CLI) is a severe peripheral vascular disease with high risk of amputation, high morbidity and mortality. Approximately 120,000 “lower” extremity amputation procedures are performed annually in the US. The annual cost for these patients is estimated at $4 billion. Therefore, there is a significant unmet medical need to develop new therapies for CLI. We propose to develop a novel human iPSC-based cell therapy to treat CLI, from which patients in California will benefit.
Funds Requested	$1,412,613
GWG Recommendation	(1-84): Not recommended for funding

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 scientific 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	• If successful, the candidate would significantly increase the likelihood of developing a stem cell-based therapy that would greatly improve patient care in critical limb ischemia (CLI).
No: 11	• It is not clear that this proposal would add substantial new insights that would impact CLI. • It is not clear that there is any reason to anticipate that the iPSC-derived endothelial cells are superior to other cells that are already in more advanced studies.
GWG Votes	Is the rationale sound?
Yes: 2	• More preliminary data is needed.
No: 13	• It is not clear that the proposed cells are significantly better than other cell types used before. • Extensive preliminary data is presented which supports the basis and objectives of the study in part. However, functional preliminary data is needed.
GWG Votes	Is the proposal well planned and designed?
Yes: 0	*none*
No: 15	• The experimental design lacks clarity. The methods refers to growing the cells under hypoxia. However, if this is not kept constant throughout preparation the cells will undergo “reperfusion injury” which will affect phenotype and differentiation. • The proposal would benefit from more detailed functional analyses as the functional outcomes for some experiments are not clear. The follow up period is short and will make it difficult to evaluate long-term benefits, which is critical for translation to humans. • The doses and times of administration appear to be different between Milestones 3 and 4 which will not allow comparisons to be made and the justification for cell numbers and timing is not clear. • For the combination studies, it is unclear how the vascular progenitors and hiPSC-ECs will be distinguished from each other.
GWG Votes	Is the proposal feasible?
Yes: 4	• The proposed experiments can be conducted in the proposed time frame.
No: 11	• The project is feasible within the timescale proposed. However, there is some concern regarding the investigator productivity and independence as only two first/senior author papers have been generated in the last 8 years.

Application #	DISC2-11117
Title (as written by the applicant)	Stabilized Percutaneous Stem Cell Transendocardial Delivery Catheter
Research Objective (as written by the applicant)	The transendocardial delivery catheter (TEDCath) safely and reversibly attaches to the endocardium to enable safe and effective delivery of human stem cells to the myocardium.
Impact (as written by the applicant)	TEDCath overcomes the limitations of currently available delivery devices that do not meet the level of clinical and technical performance needed to translate human stem cell therapies for heart failure.
Major Proposed Activities (as written by the applicant)	• Validate design inputs, design requirements with stem cell experts and fabricate initial device prototypes (V1) for bench top testing. • Evaluate functional performance of V1 prototypes in bench top tests. Design and develop V2 prototypes based on bench top testing results. Fabricate the V2 prototypes for in vivo testing. • Evaluate V2 prototypes in an initial in vivo study. Quantify cell retention rates of doses of cells delivered with the device. Design, develop, and fabricate V3 prototypes based on results. • Evaluate V3 prototypes in a 2-cohort comparison study: TEDCath vs intracoronary infusion cell delivery method. Quantify cell retention rates and cell distributions for each cohort. • Consult with regulatory consultant for pre-IDE preparation. Write final report. Identify and apply for funding for "Progression Event" to translational development stage.
Statement of Benefit to California (as written by the applicant)	The citizens of California have invested generously in stem cell research and hope to make a difference in diseases like heart failure, which is a leading cause of death in the United States. Researchers have made progress in developing stem cell therapeutics for heart failure, but devices are needed that can safely and effectively deliver these therapeutics. Our proposed delivery catheter can help stem cell therapies reach their great potential for the treatment of heart failure.
Funds Requested	$641,345
GWG Recommendation	(1-84): Not recommended for funding

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 scientific 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	*none*
No: 11	• It is not clear that this delivery system has potential to change the picture for disease modification, despite the large unmet need in heart failure. • If successful, the impact would be good, but the significance is tempered by concerns about efficacy of this approach for treatment of cardiological dysfunction. • Cell delivery is a key aspect for the translation of cell therapies. However it is unclear that short-term cell retention is due to delivery and not to lack of cardiac regenerative potential of transplanted cells. • In the animal model, a one-day follow up is not sufficient. • Adipose derived stem cells are not the cell type which should be used.
GWG Votes	Is the rationale sound?
Yes: 2	• It is not clear the approach is significantly different scientifically from similar efforts in the past.
No: 13	• There as some concerns that the approach does not have a potential for a robust therapeutic effect. • It is not clear that the catheter provides a significant improvement. • There are some concerns that adipose stem cells are not the best choice. • A major weakness is the choice of cells to be used, which are not endowed with cardiac regenerative potential, rendering results meaningless.
GWG Votes	Is the proposal well planned and designed?
Yes: 0	*none*
No: 15	• The catheter should be compared to other catheter-based delivery models. • The assay only a short time after injection is of limited value. • Major issue is the target cell population, which does not have cardiac regenerative potential. There are also issues with time points and interpretation.
GWG Votes	Is the proposal feasible?
Yes: 9	• The investigators have the required expertise. • It may be feasible, but significance and impact are low.
No: 6	*none*

Application #	DISC2-11155
Title (as written by the applicant)	Induced Pluripotent Stem Cells for Ocular Surface Regeneration
Research Objective (as written by the applicant)	Our aim is to create limbal epithelial stem cells differentiated from patient-derived induced pluripotent stem cells in order to cure blindness in patients by regenerating their ocular surface.
Impact (as written by the applicant)	There are no durable treatments for bilateral limbal epithelial stem cell deficiency patients. Autologous iPSC based limbal stem cell replacement would revolutionize therapy and restore vision.
Major Proposed Activities (as written by the applicant)	• Creation of patient-derived induced pluripotent stem cell lines for banking • Autologous induced pluripotent stem cell differentiation into limbal epithelial stem cells • Selection of biomatrix for limbal epithelial stem cell grafts • Transplantation of limbal epithelial stem cell grafts into an ocular injury animal model
Statement of Benefit to California(as written by the applicant)	Limbal stem cell deficiency is a leading cause of untreatable corneal blindness among the almost 40 million Californians. Our research to create transplantable autologous corneal stem cells would allow treated child and adult patients to return to school and work, no longer afflicted by this painful, blinding disease. In addition to the health care and social services savings this cure would bring, considerable investment in these technologies would attract jobs and other revenue to our state.
Funds Requested	$1,415,016
GWG Recommendation	(1-84): Not recommended for funding

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 3	• Corneal blindness affects millions worldwide. • Proposal is novel — A reviewer could not find other publications showing transplantation of stem cell derived limbal epithelial cells so this would be pioneering work. However, at least one other reviewer claims there are such publications.
No: 12	• The lack of detail concerning differentiation protocols and lack of rationale for differentiation medium is a concern. • There is an extensive literature (much of which the PI fails to cite) on the generation of corneal limbal epithelial cells and GMP protocols although, to my knowledge, clinical trials have yet to be performed. Human allantoic membrane has been extensively used, and proven clinically, for limbal stem cell transplantation. Thus, it is not clear how much additional information this study will provide.
GWG Votes	Is the rationale sound?

Yes: 5	• Basic scientific plan is appropriately simple and straightforward. Get tissues, make iPSCs, differentiate iPSCs to limbal epithelial cells, and transplant.
	• Grant crafting could be improved:
	  ◦ All available page space should be used unless all possible anticipated concerns of review panel have been addressed.
	  ◦ A thorough review of literature, alternative plans/pitfalls, and state of the art should be presented.
	  ◦ Carefully look for typos. e.g., 2019 as a date in the biosketch.

No: 10	• It is not clear how much additional information the study will provide. • There is insufficient preliminary data to support the feasibility of the proposal. • Limited preliminary data is provided in 4 figures. The PI demonstrates the ability to reprogram human dermal fibroblasts to iPSC in Fig 2; Fig 3 is the work of a different investigator; Fig 4 & 5 show only limited support for the PI's approach.
GWG Votes	Is the proposal well planned and designed?
Yes: 1	• The team is strong but needs to make a careful supporting case for the strength of the team because on paper they have less experience and publications than other teams. • It would be particularly important to increase preliminary data and review literature and alternative approaches to demonstrate mastery and expertise in this area.
No: 14	• The experimental plan lacks details; there is a superficial description of the experimental approach which has led to this section being 1.5 pages shorter than expected. • It is unclear how much expertise the PI has in the proposed study and several limitations in the experimental design were identified. • In the study design for aim 2, the investigators seem to have little idea what media to use and much seems to be based on what is already published. It is unclear what "various conditioned medium" actually means. They propose to determine the differentiation protocols using dermal fibroblast iPSC, and it is unclear why they do not start with cells they consider more genotypically relevant. • The organ culture component could be better validated on human eyes which are utilized for similar projects in a number of labs. The use of a debridement model in the organ culture and an alkali burn model in the in vivo model seems to lack of consistency. It is unclear whether there will be an immune response putting human cells in the rabbit eye. • The biomatrices proposed are those which have previously been reported in the literature, many of which are already in clinical use.
GWG Votes	Is the proposal feasible?
Yes: 3	• It should be possible to do all four aims. But more clarity on exactly what the differentiation protocol is and how it compares to other published protocols would help remove any uncertainty.

No: 12	• The lack of preliminary data makes the feasibility of the project uncertain. • The PI, a physician-scientist, is a recently appointed assistant professor having previously been an associate professor at a different institution. Productivity is modest with senior author papers over the last 5 years being either reviews or in low impact ophthalmology journals. The PI has minimal experience in stem cell biology and corneal cell biology.

Application #	DISC2-11164
Title (as written by the applicant)	Breast Cancer Post-Radiation Skin Injury Repair
Research Objective (as written by the applicant)	To help patients with breast cancer have better surgical reconstruction outcomes, we developed a rodent model of treating skin irradiated over a tissue expander with human adipose-derived stem cells.
Impact (as written by the applicant)	Breast cancer patients undergo reconstruction after postmastectomy radiotherapy at high rates, but 50% will have complications. Novel approaches to improve results with irradiated tissue are crucial.
Major Proposed Activities (as written by the applicant)	• Assess impact of fat grafting+/-human adipose derived stem cells (AMSCs) on histological and mechanical markers of skin health undergoing tissue expansion, using our immune deficient rat model, novel expanders & measurements • Determine the extent to which AMSCs impact pliability of skin irradiated over a tissue expander, using a cutometer to measure the skin pliability of the rats in all groups weekly after radiation • Prepare all SOPs for human AMSC expansion, using GMP-compliant methods and reagents, for future rapid transfer to GMP manufacturing. Five batches of AMSCs will be screened and potency assays developed • Prepare efficacy and initial safety data using good laboratory practices, in support of a pre-pre-IND submission to the FDA to determine what definitive studies will be needed for IND and future trial
Statement of Benefit to California (as written by the applicant)	Half of the patients in California undergoing breast reconstruction after postmastectomy radiotherapy will have a complication. Irradiated skin has diminished pliability, decreased vascularity, and poor wound healing. We are using human adipose-derived stem cells to improve skin changes and minimize post-operative complications. This will significantly reduce patient morbidity and cost to patients and health systems in California while improving patient and provider satisfaction.
Funds Requested	$1,078,806
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: --

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

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

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific 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 seems to be confusion on what will be tested in the proposed experiments. The proposal never tests stem cells by themselves but instead uses them in the context of fat/anunknown mixture of cells.
No: 10	• The chances that this will have an impact are not well substantiated because there is not good data showing that adipose stem cellls (ASCs) improve outcomes for patients. • The likelihood of success is moderate. ASCs have been shown to secrete various cytokines and growth factors that have beneficial effects on wound healing, but there is little mechanistic basis to suggest they will significantly improve autologous fat transfer following postmastectomy radiotherapy (PMRT).
GWG Votes	Is the rationale sound?
Yes: 1	• The tools they've described such as the tiny expanders and the cutometer are impressive. • There is a nice hypothesis that probably needs more data to suggest it.
No: 13	• The rationale for the use of adipose-derived stem cells is unclear. • There is little scientific rationale for why or how ASCs might influence implant-based breast reconstruction following PMRT. • The proposal lacks preliminary data on the role of ASCs in this system. • No controls are included for most experiments.
GWG Votes	Is the proposal well planned and designed?
Yes: 1	• The proposal is easy to understand and controls in the rats are included. • How this will extend to humans is not realistic and they suggest using just one cell line to test if there is an effect of ASCs is a weakness. This needs to be replicated several times.
No: 13	• The project is well-designed to test the hypothesis that fat plus ASCs improve skin mechanical properties and histology following radiation. • The experiments can be completed but it is unclear if enough information will be obtained so that the team can move the experiments into clinical trials. • There is concern with only using a single batch of cells to test for the efficacy. • Additional characterization of what will happen to the injected stem cells is required. It is unclear if the cells will spread, and unclear why marked stem cells are not used. • Milestone 3 is not developed in the proposal (Development of Master and Working Cell Banks of human MSCs) • Cell banking activities are not yet justified.
GWG Votes	Is the proposal feasible?
Yes: 4	• Milestone 1 and 2 tasks and success criteria are clear and aligned with the goals of the proposal. • Good team but insufficient expertise.
No: 10	• The project can be done in two-year timeframe. • Isolating AMSCs that have an effect is unlikely.

Application #	DISC2-11115
Title (as written by the applicant)	Immuno-oncolytic Therapy Targeting Cancer Stem Cells of Glioblastoma
Research Objective (as written by the applicant)	Our objective is to develop a therapeutic Zika virus candidate with an immuno-modulatory and oncolytic property to target glioblastoma cancer stem cells and to inhibit cancer growth.
Impact (as written by the applicant)	Glioblastoma is a deadly cancer with a 5-year survival rate of 5.1%. The proposed IMONC Zika virus-based immuno-oncolytic treatment will be a novel class of anti-cancer drug for glioblastoma patients.
Major Proposed Activities (as written by the applicant)	• Generating recombinant IMONC Zika viruses by genetic engineering. • Reconstituting the recombinant IMONC ZIKV particles and assessing their growth phenotype. • Evaluating the susceptibility of glioblastoma cancer stem cells to immunomodulatory and cancer-targeting activities of IMONC ZIKV candidates. • Completion of glioblastoma cancer stem cell line susceptibility-grading and subtyping. • Assessing therapeutic efficacy and safety of IMONC ZIKVs using a genetic mouse model. • Evaluating efficacy and safety of IMONC ZIKVs in an immunodeficient mouse model with human brain cancer, glioblastoma.
Statement of Benefit to California (as written by the applicant)	Currently, an estimated 162,341 people live with brain and other central nervous system cancers in the USA. In 2017, an estimated 16,700 deaths were due to brain cancers. According to State Cancer Profiles by NCI, California has an average annual count of 2,326 people with brain cancers, including glioblastoma. Glioblastoma is an incurable cancer with a median survival duration of 15 months. A new glioblastoma treatment would greatly benefit the people of California suffering with this cancer.
Funds Requested	$1,256,754
GWG Recommendation	(1-84): Not recommended for funding

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 scientific 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	• Glioblastoma (GBM) has an unmet need for therapies, so this is urgent area. • The creative use of Zika virus as a therapy coupled with a long history of previous research supports the concept.
No: 11	• Glioblastoma is a huge clinical problem and a targeted therapy would have impact. • Although the development of improved treatments for malignant gliomas is of great medical urgency, the idea that the proposed approach would represent an important step in that direction is not well supported.
GWG Votes	Is the rationale sound?
Yes: 0	*none*
No: 15	• It is unclear how the virus will spread and reach tumor cells, and whether there will be any toxicity. • There is not enough discussion or preliminary data to support the argument that this approach will be different than previous virus therapies. • It has been suggested that ZIKA virus is selectively toxic for stem and progenitor cells of the developing nervous system and this would offer the potential of a selectively toxic anticancer agent. However, there are problems with the primary data and also a failure to recognize limitations identified in the many years of study of viral therapies for treatment of gliomas. • The main data in relation to glioma treatment appears to be focused on a single cell line called U87. Work on gliomas has moved on enormously since the time that this line was established, and a failure to utilize any of the many cell lines currently available is a concern. • There is little support that this therapy will be safe. Previous experience must be supported by the presentation and explanation of data.
GWG Votes	Is the proposal well planned and designed?
Yes: 0	*none*
No: 15	• There is a long history of studies on attempts to use viruses to attack GBM cells and multiple problems have been identified in regards to viral spread, ability to attack the highly migratory cells, and other problems. These issues and alternatives are not appropriately considered. • The manner in which the work is been conducted suggests that although the staff may be qualified for working on ZIKA virus, more expertise is needed in regards to gliomas of the normal nervous system. • Although the claim is made that is ZIKA virus will prove safe in the nervous system of older individuals, the studies in mice that this group has conducted show tremendous toxicity of this virus in adult animals. The applicant does not address this concern directly. Analysis of cells of the normal central nervous system, which seems mandatory in light of the toxicity results obtained in mice, are not conducted.
GWG Votes	Is the proposal feasible?
Yes: 1	*none*
No: 14	• Given the effects of ZIKA virus infection on mice, there is a significant distance to be covered before they are able to demonstrate that they can complete the proposed glioma-relevant studies in vivo.

Application #	DISC2-11197
Title (as written by the applicant)	Highly Efficient Induction of Stem Cells to Endoderm
Research Objective (as written by the applicant)	We have discovered a small molecule that significantly enhances production of the liver or pancreatic tissue precursor from any patient stem cell. Liver or pancreas could be made from self tissue.
Impact (as written by the applicant)	Currently, only a small number of stem cell lines can be made into the liver or pancreatic precursor cell; however, our compound allows any stem cell to efficiently form this precursor (endoderm).
Major Proposed Activities (as written by the applicant)	• Successful transformation of many stem cells (iPS cells) into endoderm in a culture dish. • Successful transformation of many stem cells (iPS cells) into endoderm using a 3-dimensional culturing system. • Confirmation that cells treated with our compound can form functional liver tissue (hepatocytes) and pancreatic beta tissue, that would be suitable and functional for transplant. • We will identify how our compound functions at the molecular and cellular level. • We will develop a Target Product Profile to move our compound into a clinical trial.
Statement of Benefit to California (as written by the applicant)	The proposed research will speed up the development of endoderm-derived tissues including liver cells, pancreatic Beta cells and others for the purpose of both therapeutic transplantation into human patients and for research on medical diseases. This technology will enhance personalized tissue made from self. This development will significantly accelerate medical progress in California for regenerative medicine and development of targeted therapies for human diseases.
Funds Requested	$795,000
GWG Recommendation	(1-84): Not recommended for funding

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 scientific 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: 1	*none*
No: 14	• Despite difficulties, many groups have successfully generated definitive endoderm from a variety of human pluripotent stem cells. The impact of this proposal is incremental at best. • It is not clear whether this approach is really necessary; the statement that most cell lines fail endoderm differentiation protocols requires stronger justification. Some report that cell lines require adjustment of protocols. This is different from stating that protocols do not work. Others report protocols that are active across a broad range of cell lines. PI's review of literature is selective, and the preliminary data to support this key contention is feeble.
GWG Votes	Is the rationale sound?
Yes: 0	*none*
No: 15	• The nature of the key compound is not discussed, therefore the rationale unclear. • There is little evidence that the compound will enhance endoderm differentiation of a majority of cell lines; Figure 3 is anecdotal. • A strength is that a compound has been found that apparently shows the desired activity. However, insufficient specific preliminary data presented, almost all data presented is qualitative. • The applicant chooses not to identify the compound, which comes from a set of FDA-approved drugs and thus should have at least one known target. The rationale for mechanism of action studies is therefore severely flawed.
GWG Votes	Is the proposal well planned and designed?
Yes: 1	*none*
No: 14	• The reliance on in vivo transplantation for hepatocyte maturation means that this approach is unlikely to surmount a key hurdle to in vitro use of cells, namely maturation. • The mechanism of action of the compound is unknown. • Mechanism of action studies are important but very broadly based, lacking in focus, and may yield only correlations. • A clearer quantitative presentation of preliminary data is needed in order to set appropriate milestones. For example, it appears at one point the applicant claims all 18 test cell lines have already been shown to respond to the compound, obviating the need for most of the proposed studies. • It is not clear that the compound will work across the majority of cell lines and there is no real alternative if it does not.
GWG Votes	Is the proposal feasible?
Yes: 2	*none*
No: 13	• The preliminary data is not strong. • The PI track record in stem cell research is limited. • It is not clear how this can lead to a product, beyond publishing data on the identity of the compound and its activity.

Application #	DISC2-11057
Title (as written by the applicant)	Characterization of a Novel Enzyme and Its Inhibitors in iPSC-Parkinson's Disease Models
Research Objective (as written by the applicant)	An iPSC-Parkinson's disease (PD) model will be used to study a novel enzyme and its small molecule inhibitors. With success, a PD drug Development Candidate will be ready for pre-IND activities.
Impact (as written by the applicant)	Current PD drugs only alleviate symptoms; the disease progression is unchanged. Upon success, we will have generated a Development Candidate that will ultimately slow progression of PD.
Major Proposed Activities (as written by the applicant)	• Characterize a-synuclein nitration and neuronal dysfunction in iPSC-PD model(s). • Characterize and demonstrate the role of the Synuclein Nitrase in a-synuclein nitration and neuronal dysfunction in iPSC-PD model(s). • Demonstrate efficacy of Synuclein Nitrase inhibitors in iPSC-PD model(s). Develop and identify a Development Candidate for PD that inhibits a-synuclein nitration and neuronal dysfunction.
Statement of Benefit to California (as written by the applicant)	In California, nearly 180,000 people live with PD. Currently, PD drugs do not slow the course of disease. They only alleviate symptoms. This means PD patients continue to deteriorate even as their symptoms are controlled. As such there is an unmet need for drugs that reduce progression of PD. Upon successful completion, we will have generated a Development Candidate that will ultimately reduce PD progression. This will improve lives not only of PD patients but also their families and caregivers.
Funds Requested	$1,196,127
GWG Recommendation	(1-84): Not recommended for funding

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 scientific 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: 2	• It would be worth pursuing the proposed line of research if there was definitive evidence for the proposed enzyme. • If they get a drug candidate, they have the resources to advance it.
No: 13	• Although this application targets an unmet medical need, insufficient data is provided to determine whether the proposed experiments would be of therapeutic relevance. • The project is based on the discovery of an enzyme that causes nitration of alpha-synuclein. No information is provided as to how specific this reaction is, what role it might play in normal cellular function, whether dopaminergic neurons are a primary target of this titration reaction, and other information that is required to consider the scientific rationale for this project. • The applicants propose testing synuclein nitrase inhibitors to inhibit α-syn aggregation and rescue dopaminergic cell damage/death. An in vivo system for translation is lacking from this protocol and would be essential to evaluate the safety of identified compounds. • The proposal only provides minimal preliminary data. The applicants state that they possess proprietary data on synuclein nitrase and its ability to add nitrate to α-syn, this is however not shown in the proposal. The vast majority of the preliminary data presented is based on the applicants' capacity to perform the proposed methodologies/assays. There is no actual data on whether the targeted drugs will yield detectable changes in these assays. • Alpha synuclein aggregation disruption is a reasonable goal, but the protein prep is not at a stage ready to proceed to a translational outcome.
GWG Votes	Is the rationale sound?
Yes: 0	*none*
No: 15	• Lack of preliminary data is a concern. The candidate molecule works in the enzyme reaction but there is no data relevant to assessing utility, safety or specificity of the molecule. • Some classical biochemistry and more protein purification is needed as critical preliminary data. Data is needed that demonstrates that this not a mix of many different enzymes/catalysts at work. • Data that iPSC models of Parkinson's disease demonstrate alpha-synuclein nitration or disease relevant neuronal dysfunction is needed. Correlated with this, data on the roles of alpha-synuclein nitration and synuclein nitrase in such outcomes is needed. • The claim to have identified a novel enzyme "alpha-synuclein nitrase" is a remarkable claim as there are, to a first approximation, no known nitrases. Some activity has been demonstrated, but data demonstrating specificity of the molecule is needed. • If there is a novel nitrase, its existence should be reflected by a molecular evolution analysis. Please provide such an analysis as preliminary data on what other organisms seem to have it and which human genes might possibly encode it, based on analyses such as Pfam.
GWG Votes	Is the proposal well planned and designed?
Yes: 0	*none*
No: 15	• This is a striking lack of cell data provided, considering the ready availability of IPSC-derived dopaminergic neurons and the availability of an enzyme inhibitor. • More preliminary data is needed. Existence of enzyme needs to be proven and purified before a translational proposal is developed.
GWG Votes	Is the proposal feasible?
Yes: 1	*none*
No: 14	• The absence of appropriate biological data makes feasibility difficult to evaluate. • As there is no demonstration that the core hypothesis is anything more than a speculation, there are many potential pitfalls. • The team needs more expertise in molecular evolution and biochemistry, particularly in enzymatic purification.