QUEST AWARDS

10/11/18

$19,007,245 GWG RECOMMENDED

$865,282 AMOUNT AVAILABLE

$9,134,718 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	A	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	A	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	A	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 iPSC-derived 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	$865,282	W	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	A	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	$865,282	A	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	A	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	A	85	83	4	75	90	9	5	Y	N	Frontotemporal dementia	Cell therapy	iPSC-derived microglia to treat progranulin deficiency

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

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	• 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*