APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Resubmission	Previous CIRM Funding	Disease Indication or Area of Impact	Product Type	Approach
DISC2-13400	Targeted Immunotherapy-Based Blood Stem Cell Transplantation	**$1,341,910**	**Y**	**95**	94	3	89	97	14	0	N	Y	Malignant blood disorders	Biologic	Antibody that targets and triggers removal of native hematopoietic stem cells to enable healthy HSC transplant
DISC2-13505	Combating Ovarian Cancer Using Stem Cell-Engineered Off-The-Shelf CAR-iNKT Cells	**$1,404,000**	**Y**	**90**	90	0	89	91	14	0	Y	Y	Ovarian cancer	Cell and gene therapy	Development of a CAR-iNKT cell therapy targeting mesothelin in ovarian cancer cells
DISC2-13515	A treatment for Rett syndrome using glial-restricted neural progenitor cells	**$1,402,240**	**Y**	**90**	90	0	90	90	13	0	Y	Y	Rett syndrome	Cell therapy	Neural progenitor cells derived from pluripotent stem cells to treat Rett syndrome
DISC2-13454	Targeting pancreatic cancer stem cells with DDR1 antibodies.	**$1,425,600**	**Y**	**90**	89	2	85	92	14	0	N	N	Pancreatic cancer	Biologic	Antibody that targets pancreatic cancer stem cells to enhance effectiveness of chemotherapy
DISC2-13483	Enabling non-genetic activity-driven maturation of iPSC-derived neurons	**$675,000**	**Y**	**90**	89	3	84	95	14	1	Y	N	Neurological disorders	Tool	Technology platform to speed up and improve generation of iPSC-derived neurons and organoids
DISC2-13405	Hematopoietic Stem Cell Gene Therapy for Alpha Thalassemia	**$1,323,007**	**Y**	**90**	88	3	80	90	14	1	N	N	Alpha thalassemia	Cell and gene therapy	Development of an autologous, gene-corrected hematopoietic stem cell therapy to treat alpha thalassemia
DISC2-13507	CAR T cells targeting abnormal N-glycans for the treatment of refractory/metastatic solid cancers	**$1,414,800**	**Y**	**90**	88	4	75	90	14	1	Y	N	Relapsed, refractory or metastatic solid cancers	Cell and gene therapy	Develop a CAR T cell therapy to kill solid cancers by targeting a tumor associated carbohydrate antigen
DISC2-13463	Drug Development of Inhibitors of Inflammation Using Human iPSC-Derived Microglia (hiMG)	**$1,658,123**	**Y**	**90**	88	5	80	94	11	3	Y	N	Alzheimer's disease, Parkinson's disease	Small molecule screen	Screen for small molecule drugs that inhibit inflammation to treat neurodegenerative disease
DISC2-13390	Cardiac Reprogramming Gene Therapy for Post-Myocardial Infarction Heart Failure	**$1,215,000**	**Y**	**88**	88	1	85	90	13	0	N	Y	Heart failure	Gene therapy	Gene therapy that targets cardiac fibroblasts and reprograms them into myocardiocytes to restore heart function
DISC2-13417	AAV-dCas9 Epigenetic Editing for CDKL5 Deficiency Disorder	**$1,429,378**	**Y**	**88**	88	2	83	90	13	1	N	N	Infantile epilepsy	Gene therapy	A gene therapy that reactivates CDKL5 using epigenetic editors
DISC2-13415	Defining the Optimal Gene Therapy Approach of Human Hematopoietic Stem Cells for the Treatment of Dedicator of Cytokinesis 8 (DOCK8) Deficiency	**$1,386,232**	**Y**	**85**	85	0	85	85	14	0	N	Y	DOCK8 Deficiency	Gene therapy	Autologous human hematopoietic stem cells modified through either lentiviral gene addition or CRISPR/Cas9 based gene editing
DISC2-13498	Bioengineering human stem cell-derived beta cell organoids to monitor cell health in real time and improve therapeutic outcomes in patients	**$1,198,550**	**Y**	**85**	85	2	80	87	11	4	Y	N	Type 1 diabetes	Cell therapy	Generate nanoprobe-containing stem cell-derived human beta cells that can be monitored in real time for viability
DISC2-13469	Novel antisense therapy to treat genetic forms of neurodevelopmental disease.	**$1,180,654**	**Y**	**85**	85	2	80	90	10	3	Y	Y	Neurodevelopmental diseases	Biologic	Evaluation of antisense oligos for treating neurodevelopmental disorders using patient-derived stem cells
DISC2-13428	Therapeutics to overcome the differentiation roadblock in Myelodysplastic Syndrome (MDS)	**$1,244,160**	**Y**	**85**	84	4	70	87	13	2	N	N	Myelodysplastic syndromes	Small molecule	Optimize small molecule candidate that acts on diseased hematopoietic stem cells to stimulate differentiation
DISC2-13456	Novel methods to eliminate cancer stem cells	**$1,384,347**	**Y**	**85**	84	2	80	85	13	2	Y	N	Leukemia	Small molecule screen	Screen for small molecule drugs that inhibit leukemic cancer stem cells
DISC2-13441	A new precision medicine based iPSC-derived model to study personalized intestinal fibrosis treatments in pediatric patients with Crohn’s disease	**$776,340**	**Y**	**85**	84	3	75	88	10	5	Y	N	Crohn's disease	Diagnostic tool	Develop a tool using patient specific iPSC-derived intestinal organoids to identify personalized antifibrotic treatments
DISC2-13512	Modified RNA-Based Gene Therapy for Cardiac Regeneration Through Cardiomyocyte Proliferation	**$1,565,784**	**Y**	**85**	84	2	80	87	10	5	Y	N	Heart failure	mRNA biologic	Modified mRNA encoding cell cycle regulators as a therapy for cardiac regeneration
DISC2-13510	An hematopoietic stem-cell-based approach to treat HIV employing CAR T cells and anti-HIV broadly neutralizing antibodies.	**$1,143,600**		**84**	84	2	80	90	7*	7	Y	N	HIV	Cell and gene therapy	Develop a CAR T and B cell therapy expressing broadly neutralizing antibodies against HIV

APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Resubmission	Previous CIRM Funding	Disease Indication or Area of Impact	Product Type	Approach
DISC2-13475	Developing gene therapy for dominant optic atrophy using human pluripotent stem cell-derived retinal organoid disease models	**$1,345,691**		**84**	83	2	79	85	7*	8	Y	N	Dominant optic atrophy	Gene therapy	Use PSC-derived human retinal organoids to evaluate efficacy of a gene therapy
DISC2-13413	In Utero Treatment of Duchenne Muscular Dystrophy with Non-viral Gene Editing	**$1,221,980**		**84**	81	5	70	85	6*	8	N	N	Duchenne muscular dystrophy	Gene therapy	Develop a lipid nanoparticle/mRNA complex that can safely and efficiently edit muscle stem cells in utero
DISC2-13442	Microgel encapsulated iPSC-derived notochordal cells to treat intervertebral disc degeneration and low back pain	**$1,342,606**		**83**	83	3	80	86	6*	8	N	Y	Intervertebral disc degeneration	Cell therapy	Develop an injectable microtissue-encapsulated iPSC-derived notochordal cell therapy to treat disc degeneration
DISC2-13502	Excitatory spinal interneurons from human pluripotent stem cells to treat spinal cord injury	**$1,560,728**		**83**	83	3	77	86	5	10	Y	Y			
DISC2-13438	HIV therapeutics composed of lipid nanoparticle-mRNA complexes that edit the CCR5 gene	**$1,015,476**		**82**	83	4	80	90	4	11	N	N			
DISC2-13514	Engineered Human Stem Cell-Derived Pancreatic Islets Encapsulated in a Thin Film Device for Patients with Type 1 Diabetes	**$1,458,825**		**82**	81	4	75	85	4	11	Y	Y			
DISC2-13396	Reprogramming Somatic Cells into iPSCs Engineered with an Anti-PSCA CAR to Develop Allogeneic Off-the-Shelf Cell Therapy to Treat Pancreatic Cancer	**$1,358,100**		**82**	81	2	75	85	1	14	N	N			
DISC2-13488	Targeted Biocoated Mesoporous Silica Nanoparticle Delivery of an RNAi Therapeutic to Cancer Stem Cells in Recurrent/Refractory Ovarian Cancer Models	**$847,103**		**80**	81	1	80	83	0	15	N	Y			
DISC2-13532	Development of next-generation human cerebellar organoids to model hereditary cerebellar ataxias	**$834,000**		**80**	79	2	75	83	0	13	N	N			
DISC2-13439	Establish master iPSC for targeted large-cargo integration and its application in developing safe and efficacious iPSC-CAR-iNK allogeneic product	**$1,128,350**		**80**	77	4	70	83	0	14	N	N			
DISC2-13409	Developing CRISPR-Cas9 genome editing as a therapy for dyskeratosis congenita (DC) and related telomere biology disorders (TBDs)	**$1,083,715**		**75**	76	2	75	80	0	14	N	N			
DISC2-13393	Development of novel small molecules against cancer stem cells in solid cancers	**$1,404,000**		**75**	74	4	65	80	0	15	N	N			
DISC2-13450	Generation of polarization-restricted human iPSC-derived macrophages to reprogram the multiple myeloma tumor microenvironment	**$1,425,600**		**75**	74	2	70	75	0	13	N	Y			
DISC2-13524	Engineered injectable pre-vascularized microporous implants for neural stem cell transplantation after stroke	**$1,444,500**		**75**	74	3	70	77	0	13	N	N			
DISC2-13458	An iPSC-derived neural progenitor cell product with inducible GDNF expression for treatment of ALS	**$1,355,506**		**75**	73	3	70	75	0	14	N	Y			
DISC2-13414	An interactive data resource for hypothesis testing in stem cell single-cell gene expression and validation of the results with brain organoids	**$690,280**		**75**	72	6	60	80	0	14	N	Y			
DISC2-13522	A Novel Therapy for Sanfilippo B	**$1,426,350**		**73**	73	4	70	80	0	14	N	N			
DISC2-13478	ANCHOR for ART-SCID: All Non-Viral CRISPR-Cas Homology-directed Repair as First-in-Class Cure for Artemis-deficient Severe Combined Immunodeficiency	**$1,130,212**		**70**	73	6	65	85	1	12	N	N			

APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Resubmission	Previous CIRM Funding	Disease Indication or Area of Impact	Product Type	Approach
DISC2-13495	Investigate vision protection after subretinal injection of a combined cell and gene product at the clinically relevant stage of retinal degeneration	**$1,357,802**		**70**	71	3	70	80	0	15	Y	Y			
DISC2-13437	A small molecule therapeutic to differentiate cancer stem cells	**$1,425,600**		**70**	70	3	60	75	0	13	N	N			
DISC2-13455	Development of small molecules to restore function in neurons from Intellectual Disability Syndromes	**$1,306,000**		**70**	70	4	65	75	0	13	Y	N			
DISC2-13541	Developing anti-SEMA4D antibody drug conjugate as a prophylactic therapy for brain metastasis	**$1,417,700**		**70**	69	5	55	80	0	14	N	N			
DISC2-13432	Human Induced Pluripotent Stem Cell-Derived Endothelial Cells for Treatment of Peripheral Arterial Disease	**$1,043,000**		**70**	68	7	60	80	0	15	N	N			
DISC2-13535	Targeting glioblastoma using human pluripotent stem cell-derived neural or glial progenitor cells loaded with oncolytic virus	**$1,358,100**		**65**	67	6	60	85	1	14	N	Y			
DISC2-13533	Gene therapy vector correcting endoplasmic reticulum stress and GABA uptake defect in myoclonic atonic epilepsy	**$1,283,566**		**65**	66	5	60	80	0	13	Y	N			
DISC2-13398	Bioinspired noncoding RNA chemical entity for Duchenne muscular dystrophy	**$1,397,412**		**60**	59	6	50	70	0	15	N	Y			
DISC2-13519	Drug Discovery for Duchenne Muscular Dystrophy Using Patient-Derived Human iPSCs	**$1,215,000**		**-**	**-**	**-**	**-**	**-**	0	15	N	N			
DISC2-13491	An Engineered Exosome Nanocarrier System for Delivering Gene Therapy to Lung Cancer Stem Cells	**$1,201,524**		**-**	**-**	**-**	**-**	**-**	0	15	N	N			
DISC2-13506	Bi-functional immune therapy for lung cancer	**$1,287,936**		**-**	**-**	**-**	**-**	**-**	0	15	N	N			

*** Minority Report**

Application #	DISC2-13400
Title (as written by the applicant)	Targeted Immunotherapy-Based Blood Stem Cell Transplantation
Research Objective (as written by the applicant)	An engineered antibody construct that targets and recruits immune cells to kill diseased blood stem cells, including leukemia stem cells, so that healthy stem cells can replace the diseased ones
Impact (as written by the applicant)	An antibody that can direct immune cells to kill diseased stem cells would make stem cell transplant safer, more accessible, and more effective for the treatment of many life-threatening blood disorders
Major Proposed Activities (as written by the applicant)	• Design and produce antibody constructs that can direct immune cells to bind to and kill normal and malignant blood stem cells • Test the candidate antibody constructs in cell culture assays to determine/rank which constructs are the most potent at killing target cells • Select the top candidate constructs for testing in mice that have been engrafted with malignant human stem cells • Perform scale up production of the top candidates • Test administration of top constructs in mice that have been engrafted with malignant human stem cells to determine if the treatment results in permanent eradication of the diseased cells • Treat mice engrafted with malignant human stem cells with combined construct plus transplants of normal human stem cells to determine if diseased cells are eradicated and replaced by healthy stem cells
Statement of Benefit to California (as written by the applicant)	Almost 10,000 Californians with blood diseases received a blood stem cell transplant (SCT) in the past 10 years. Although SCT can be curative, many suffer serious and life-threatening side effects due in part to toxic chemotherapy and radiation used during SCT. Thus, transplant is costly and unavailable to thousands of underserved Californians with blood diseases. Replacing toxic chemoradiation with a non-toxic antibody can minimize the hardships of SCT and expand its availability to the underserved.
Funds Requested	$1,341,910
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 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	3
Highest	97
Lowest	89
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 13	• The proposed work will test novel Bispecific NK-cell engagers (BiKE) and Trispecific NK-cell engagers (TriKE) to address an important unmet clinical need, which is the need for less toxic and more effective ways to eliminate malignant hematopoietic stem cells (HSCs) prior to HSC transplant (HSCT). • The applicant provides exciting preliminary evidence in support of the main approach, which is to target CD117 (Kit receptor) on HSCs as a means to eliminate malignant cells but also to aid in the clearing of normal HSCs to increase HSCT graft acceptance. • Yes. If these new therapeutic candidates are shown to be successful in the proposed studies, then there is a high degree of likelihood that these findings will lead to new stem cell-based therapies to improve patient care. • This agent is a first of its kind, and has a broader impact beyond leukemia with potential use in patients with other malignant and non-malignant conditions for whom HSCT is indicated.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• Yes: proposed project stems from previous CIRM-funded work, which was tested in two clinical trials (CD117 mAb) with excellent safety profiles and feasibility of allowing patients to proceed to HSCT (even in the outpatient setting; published). • The applicant has also published sound preclinical work showing that leukemia HSC clones express CD117 at high levels. • The investigators have established a novel preclinical model to test the potency of candidate therapeutic agents that target these abnormal HSC clones. • The main rationale for the work is solidly based on pre-clinical and current clinical studies that support to the notion of targeting CD117 on HSCs to enable HSCT. • The preliminary data are very compelling and also highlight the need for the proposed therapy in cases of high-risk myelodysplastic syndrome (MDS), where single agent treatment with anti-CD117 appears to not fully eradicate disease in NSG mouse models. Of note, this high-bar mouse model will be used to test the new BiKE and TriKE constructs. • The idea to use NK vs. T cells based on preventing pancytopenia and preventing slow engraftment and represents a thoughtful and unique aspect of the proposal. • The proposed work will enable therapies using human HSCs. • The project will also enable HSCT in patients that would otherwise be ineligible.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**

Yes: 13	• The proposed work is outlined as three main aims.
	  ◦ The first aim is focused on generating novel BiKE and TriKE constructs, that will engage CD177 on HSCs and CD16 (and NKp46) NK cells. This aim also proposes to create BiTE constructs to engage CD177 and CD3e on T cells, as controls to contrast the efficacy of NK cell targeting. This aim will test the expression and in vitro engagement of target cells.
	  ◦ Aim 2 will address the function of the new constructs in targeting and killing of model MDS cell lines using a human NK cell line.
	  ◦ Aim 3 will test the function of the new constructs using an in vivo HSC engraftment model system.
	  ◦ A key aspect of Aim 3 is the adoptive transfer of human NK and T cells to the NSG mice already engrafted with HSCs or MDS HSCs. This is critical for the

	effectiveness of the BiKE and TriKE constructs to be tested within this humanized mouse model. This step is also important in part b of this aim, wherein the applicant will test the ability of the treatment to clear high risk MDS HSC engraftment and allow for new HSCT to take place. This serves as an excellent test of the main hypothesis and validation of the approach. ● **Yes:** the proposed studies use a sophisticated mouse model, and are supported with robust preliminary evidence (novel in vivo model to assess the efficacy of different targeted therapeutic approaches at eliminating leukemia HSCs; sound development of of engineered anti-hCD117-NK constructs with proposal for selection of most cytotoxic. ● For this project, the applicant plans to harness the cytotoxicity of NK cells (well-established including in clinical settings) and ADCC by creating BiKE/TriKEs that engage CD117 present on leukemia clones as well as HSCs (for use as tumor elimination and conditioning enabling transplant). The proposed candidate therapeutic will utilize the targeting function of anti-hCD117 Abs and recruit and activate NK cells with the goal to enhance clearance of the endogenous HSC. ● The proposed work is well-structured and of very high quality. ● The applicant provides a set of carefully considered pitfalls and alternative approaches. ● There is a high degree of innovation and elegance in the proposed work.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 13	● The core team is composed of the PI, principal scientist, project manager, lab manager and research assistants. This team will meet weekly to plan, design experiments, review and present data. Consultants and CRO's will be contacted as needed. They will hold larger monthly meetings which will include data review and experiment planning, and which can include consultants/CRO. ● The institution provides a highly interdisciplinary environment well suited to support the success of the project. The lab is located within the medical center, adjacent to collaborating investigators. ● The CRO will generate the engineered antibody constructs. The team has identified an excellent CRO with 10 years of experience in antibody sequencing, engineering and recombinant expression. The CRO offers royalty free services. They have sequenced and manufactured thousands of hybridomas and antibodies, including engineered antibodies and have journal citations. ● The applicant has engaged the CRO on initial designs and is proceeding through the contracting phase. ● Yes, the proposed aims are well-structured and feasible within the outlined timeframe. ● Appropriate project management/co-investigator support are planned.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	● **Yes:** the proposed product, if successful, will help to address the bottleneck wherein patients from underserved groups are unable to access transplants due to medical, financial or logistical barriers based on conditioning regimens or transplant plan. ● The proposal includes detailed discussion of incorporation of DEI core values into research plan, lab, center, and institution. ● Yes, the applicant points out and addresses these factors in the proposal.
No: 0	*none*

Application #	DISC2-13505
Title (as written by the applicant)	Combating Ovarian Cancer Using Stem Cell-Engineered Off-The-Shelf CAR iNKT Cells
Research Objective (as written by the applicant)	Hematopoietic stem cell (HSC)-engineered allogeneic mesothelin-targeting CAR-iNKT (AlloMCAR-iNKT) cells
Impact (as written by the applicant)	Treatment of ovarian cancer
Major Proposed Activities (as written by the applicant)	• Milestone 1. Production of the AlloMCAR-iNKT cells • Milestone 2. Characterization of the AlloMCAR-iNKT cells • Milestone 3. Delivery of the new therapeutic candidate
Statement of Benefit to California (as written by the applicant)	Ovarian cancer (OC) is the leading cause of death among women with gynecological malignancies. In the United States, California is the state with the highest incidence and mortality associated with ovarian cancer. In 2021, it is estimated that 2,550 women will be diagnosed with OC and 1,640 women will die from this disease in California. Therefore, novel therapies are urgently needed. The proposed project can potentially lead to a novel off-the-shelf cell therapy for ovarian cancer and save lives.
Funds Requested	$1,404,000
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 90

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

Mean	90
Median	90
Standard Deviation	0
Highest	91
Lowest	89
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 13	• The proposed product, mesothelin-targeting chimeric antigen receptor (MCAR) invariant natural killer T (iNKT) cells, has the potential to meet an as yet unmet need for effective natural killer (NK) cell therapy for advanced stage ovarian cancer. Invariant natural killer T (iNKT) cells cells appear to have a mesothelin-independent mechanism of tumor cell killing which, in combination with mesothelian-dependent tumor cell killing, endows MCAR-iNKT cells with greater potential efficacy than conventional MCAR-NKT. The use of MCAR-iNKT also potentially reduces the risk of graft-vs-host disease. • The proposed work builds on the applicant's currently funded project to generate hematopoietic stem cell (HSC)-derived invariant natural killer T (iNKT) cells expressing a chimeric antigen receptor (CAR), or CAR-iNKT cells, to target multiple myelomas. Here, the applicant will target ovarian cancer (OC) using a CAR against mesothelin. The proposed immunotherapy will be further improved by the addition of immune-enhancement genes (IEG) such as IL-15. • The applicant provides very exciting preliminary evidence in support of the approach, showing that allogeneic MCAR-iNKT cells have superior tumor killing activity in vitro and in vivo as compared to CAR T cells. • The successful development of allogeneic (Allo)MCAR-iNKT cells against OV would greatly impact the broader unmet medical need for better treatments for patients with solid tumors. • The proposed technology is likely to result in a candidate that could impact an unmet medical need. • The applicant has presented thoughtful options for future directions if this project is successful.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• The rationale for using mesothelin for conventional CAR-T cell therapy in ovarian cancer is established. Early phase clinical data suggest that the conventional, mesothelin-targeted CAR T is well-tolerated and shows a small efficacy signal. These clinical results bolster the applicant's rationale to continue development of immunotherapies, like the proposed product, that target mesothelin. • The main rationale for the work is solidly based on pre-clinical and current clinical work showing the effectiveness of CAR-T cells therapies. • The applicant's choice of allogeneic MCAR-iNKT cells is well-supported by the literature. • The preliminary data are very compelling and also highlight the need for the proposed therapy in cases when the target tumor antigen may be expressed at low levels, as AlloMCAR-iNKT cells appear to use multiple mechanisms to recognize tumor cells, and thus may be more reactive than conventional CAR-T cells. This aspect of the work has been much improved in the revised resubmitted application. • Preliminary studies demonstrate dual mechanisms of tumor cell killing, reduction in immunosuppressive cells, and reduced potential for GVHD. • The preliminary data provide strong support for the isolation, culture, and expansion of functionally competent iNKT cells utilizing methods developed by the applicant. • The preliminary data demonstrate superior in vitro and in vivo anti-tumor activity for the MCAR-iNKT cells, and also indicate that MCAR-iNKT have reduced risk of triggering GVHD. • The proposed project is based on sound scientific rationale. • The preliminary data are compelling and supportive of the proposed project.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 13	• The PI and team have previously developed an iNKT cell product for lymphoid malignancies. This included the development of the lentivector to be used in this study and all the evaluative measures of product functionality. Their efforts have resulted in licensure for a B-cell directed CAR-iNKT cell therapeutic for which an IND application is planned. The applicant's familiarity with every step of the development process is evident in the detailed plan for the development of MCAR-iNKT cells.

	• This is a thoughtful and rigorous research plan. Multiple features of the cell product will be directly measured (MCAR designs, suicide gene inclusion, route of administration), direct comparisons to conventional MCAR cells will be made, and mechanistic studies and rigorous in vitro and in vivo measures of efficacy/toxicity are proposed. • The project is appropriately planned and designed to meet the expected outcome of the program announcement (a candidate ready to advance to translation). This is a well-constructed, quality project. The project plan and timeline demonstrate an urgency that is commensurate with CIRM's mission. I have a minor concern regarding the lack of fully immunocompetent murine models. • A key aspect of Aim 2 is the testing different routes to perform the adoptive transfer of human AlloMCAR-iNKT cells into the PDX-NSG mice. This is critical for the effectiveness of the AlloMCAR-iNKT cells tested within this PDX mouse model. This step, together with further characterization of the AlloMCAR-iNKT cell product, serves an excellent test of the main hypothesis and validation of the therapeutic potential. • More consideration of whether there might be immunological toxicities that are unaddressable in the mouse models might have been beneficial. • More consideration of alternate targets to mesothelin could have been beneficial. This could have specifically addressed those with low-expressing ovarian cancer. This would have benefitted with a discussion of whether mesothelin expression correlates with outcome subtypes, and/or racial and ethnic patient subsets.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 13	• The application includes a feasible production and evaluation schedule with appropriate milestones. The applicant has the required expertise. • The proposed work is well-structured and very high quality. I'm impressed with the innovation and elegance in the proposed work. • The approach is feasible.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	• There are substantial race-related differences in ovarian cancer incidence and survival. Data suggest that these persist even when controlling for access to health care, though there can be little doubt that equal access to the most advanced treatments could reduce the disparity in outcome. The proposed therapeutic will make equal access to cellular therapy more likely by decreasing the cost dramatically, and decreasing the frequency of dosing. • Yes; the applicant addresses these factors in the proposal. • Yes; the project can serve the needs of underserved communities.
No: 0	*none*

Application #	DISC2-13515
Title (as written by the applicant)	A treatment for Rett syndrome using glial-restricted neural progenitor cells
Research Objective (as written by the applicant)	We developed a novel glial-restricted neural progenitor cells transplantation strategy as a treatment for Rett syndrome, reverting neuronal alterations caused by genetic mutations.
Impact (as written by the applicant)	There are no disease-modifying therapies for Rett syndrome. Our therapeutic, if successful, will be a first-in-class treatment for this devastating neurological disorder and potentially others.
Major Proposed Activities (as written by the applicant)	• Characterization of the candidate glial-restricted progenitor stem cells production. • In vitro studies of the cell transplantation in Rett syndrome brain organoids to assess the ability of the cells to revert neuronal alterations at molecular, cellular and circuit levels. • In vivo efficacy studies upon cell transplantation in the brains of a mice model for Rett syndrome to measure the cellular, physiological, behavioral and survival impact of the treatment. • Prepare and organize the next steps using large animals to assess immunogenicity, cytotoxicity and off-target effects before moving into clinical trials.
Statement of Benefit to California (as written by the applicant)	Brain disorders are responsible for more years lost to disability than any other medical condition. Rett syndrome is one of these conditions, affecting Californians independently of race/ethnicity and socioeconomic status. Our therapeutic strategy can be applied to several other neurological conditions, including Parkinson's and Alzheimer's Disease, but also autism spectrum disorders, affecting 1 in every 54 births worldwide, expanding the benefits of the development of this approach.
Funds Requested	$1,402,240
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 90

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

Mean	90
Median	90
Standard Deviation	0
Highest	90
Lowest	90
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 12	• There are no current treatments for Rett syndrome. The proposed technology takes a novel approach by providing cells to protect neurons. • Rett syndrome is a serious pediatric disorder with no available treatments. • Rett syndrome is a devastating neurological disorder. A recent gene therapy trial was stopped due to a lack of efficacy. There is a great unmet need to identify novel therapeutic approaches. • The applicant identified an astrocyte based cell therapy approach that would greatly advance the toolbox to address Rett syndrome progression and pathology. • The candidate neural progenitor cell treatment will be validated through this study which proposes a thorough preclinical assessment. • if successful, the next step would include up scaling cell production in GMP conditions (a letter from an Alpha Clinic and laboratory has been provided). Some key experiments would needed to be repeated in larger animals using a GMP version of the clinical-grade lines.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• The development of the proposed glial precursor transplantation for Rett syndrome would be useful in this syndrome and also conceivably in multiple other situations. • The rationale for trying to treat Rett syndrome by providing functional glial cells makes excellent sense based on what is known about the biology of the syndrome. • Premise for neural cell replacement is very strong based on preliminary data. • The rationale is well laid out and supported by data. • Outstanding preliminary data to understand disease and the role of the cells, including reactivation of Rett expression in these cells. • They have demonstrated successful transplantation and survival into the brains of an adult female mouse model for Rett, with indications for rescue of neuronal soma size. • There is preliminary data on transplantation of cells in a mouse model. • Excellent use of human organoid model. • A previous question of why organoids were used rather than 2D cultures was addressed by pointing out '....that brain organoids last longer than traditional 2D cultures, allowing us to longitudinally study the impact of therapeutic approaches for months rather than weeks". This seems reasonable.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 12	• The plan proceeds from in vitro assessment in human model through to animal testing. There is thorough description of studies at all phases. There is extensive consideration of possibilities for failure and means to address unexpected outcomes. • Endpoints in the organoids are well-defined and the animal experiments are clearly described and allow for analyses of pathological endpoints. • The applicant proposes different time lines of treatment for male and female animals due to the different severity and disease progressing. This is a strength of the application. • Migration and dissemination of transplanted cells is now analyzed. • The design is appropriate although it is deficient in respect to discussion on the problem of scaling and whether it will be possible to achieve enough normal cells in the diseased central nervous system to have the kind of broad impact that would be required to have a clinical benefit.

	• The applicant points out that future cells would need to be derived from cGMP hypoimmunogenic pluripotent cells that carry a suicide, fail-safe gene. This begs the question of why these cells are not used in this application thus avoiding large repeat experiments including single cell seq analysis.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 12	• The project is highly feasible and preliminary data instill confidence in the approaches. • PI is expert in this condition and a leader in stem cell/neuroscience field. • A collaborator with expertise in preclinical assessment of therapies for Rett syndrome is on the team. • Plans are in place for GMP production of the therapeutic product and there is interest from biotech. • The milestones and outcomes are likely to be achieved. • The timeline is reasonable and pitfalls are addressed. • Research pitfalls and alternative approaches are presented, with the exception of discussion of potential issues of scaling and the need to populate an entire central nervous system.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 12	• Costs of supportive care for this condition are very high and outcomes unsatisfactory. • Genetic diseases do not discriminate between communities. • Yes, males and females are use in this study. • Appropriately focused on females, project uses iPSC from diverse backgrounds but uses mice of both sexes. • The applicant acknowledges that future cell therapies are likely to be cost-prohibitive for underserved communities and propose working with a GMP-grade hypoimmunogenic iPSC cell line that would work for all patients, independent of their genetic background.
No: 0	*none*

Application #	DISC2-13454
Title (as written by the applicant)	Targeting pancreatic cancer stem cells with DDR1 antibodies.
Research Objective (as written by the applicant)	A therapeutic antibody to DDR1 for targeting pancreatic cancer stem cells to overcome resistance to chemotherapy and potentiate the treatment of advanced cancer.
Impact (as written by the applicant)	Pancreatic cancer (PDAC) is a lethal cancer that responds poorly to chemotherapy when it becomes resistant. DDR1 antagonistic antibodies (Abs) should improve chemotherapy responsiveness and may cause tumor regression as a monotherapy.
Major Proposed Activities (as written by the applicant)	• Generate monoclonal antibodies to the pancreatic cancer stem cell protein DDR1. • Identify those antibodies that are most effective in blocking DDR1 function. • Confirm that these antibodies preferentially target and destroy pancreatic cancer stem cells. • Confirm that these antibodies shrink human pancreatic cancers cells grown in mice by killing pancreatic cancer stem cells. • Select a therapeutic candidate and improve its pharmacological properties.
Statement of Benefit to California (as written by the applicant)	Pancreatic cancer (PDAC) is lethal and a leading cause of cancer deaths in California. PDAC is often detected too late when treatment prospects are poor, and few patients qualify for resection. African Americans and Hispanics are at a higher PDAC risk and may have limited access to high quality care. We will develop on antibody for destroying PDAC stem cells and preventing resistance to standard chemotherapy. The product of our research could reduce pancreatic cancer mortality and economic burden.
Funds Requested	$1,425,600
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 90

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

Mean	89
Median	90
Standard Deviation	2
Highest	92
Lowest	85
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 13	• Yes - this is a very exciting project by my read. A novel target, DDR1, with interesting biology related to cancer-associated fibroblasts, the extracellular matrix (collagen) that they make, and the progression of pancreatic cancer. • The project focuses on generating an antibody to DDR1, which intriguingly is expressed on cancer stem cells in pancreatic cancer (according to recent scRNAseq data). • Yes - the applicant proposes to generate and test several antagonistic antibodies to DDR1 to prevent its activation by MMP-cleaved collagen. The antibodies will be generated in two different ways (standard immunization of mice, including use of a DDR1 KO mouse) and by phage display. The properties of the antibodies will be tested in three different in vivo models after confirming in vitro functional blockade of DDR1. • Pancreatic cancer is a deadly disease with limited treatments options and poor 5-year survival. • A monoclonal antibody that induces internalization of DDR1 may lead to differentiation of pancreatic cancer stem cells, increasing sensitivity to chemotherapy and reducing tumor growth.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 11	• Yes - this proposal is based on very rigorous science, with well thought out controls. • The investigators' recent findings are highly supportive of the project. • Yes. DDR1 inhibition decreases tumor growth and, potentially, tumorigenesis.
No: 2	• The proposal includes weak evidence that this therapy is targeting cancer stem cells. • It is not clear that this project targets stem cells. A better justification of why the affected cells are stem cells would improve the score.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 13	• Yes. the antibody, if effective as designed and tested in the proposed data package, would likely lead to a trial. • This is a well-constructed, quality project. • Potential pitfalls with regard to antibody generation and in vivo models are discussed. One area that is not discussed is how the lead antibody would be chosen if there was not one candidate that was the obvious winner in multiple different assays (that is, if there were discrepancies between in vitro signaling changes indicating DDR1 antagonism, or if the one with the highest in vitro activities on the target had the least in vivo activity on the target). • The experimental approach to develop a DDR1-specific antibody in DDR1-KO mice is sound, especially given the homology between human and murine DDR1. A limitation to this approach is the use of C57BL/6 mice for antibody production instead of Balb/c. The investigators may consider moving the DDR1 null allele to the Balb/c background. • A phage display library will also be utilized to identify candidate antibodies with blocking and/or internalization activity against DDR1. • The application does not include a plan to evaluate the safety of DDR1 antibody against DDR1-expressing tissues, which should be added given the expression of DDR1 in brain, lung, etc.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 13	• Yes; this is a very carefully thought out plan. • This is an expert team. The Principal Investigator in particular has a tremendous track record of success, is a member of the National Academy, has made seminal discoveries in the field relevant to this project (signaling and transcription factors in GI cancers, cytokine pathways and cancer stem cells in GI cancers). h-index > 200.

	• Yes; the applicant team is well set up with the necessary resources to conduct the proposed activities. Some of the antibody generation will be outsourced to a company. • The budget is appropriate for the research proposed. • There is risk involved in funding a proposal that aims to develop an antibody and then evaluate the activity of said antibody. However, the preliminary data supports the role of DDR1 in stem phenotypes in pancreatic cancer cells.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	• Yes. Studies will include analyses of slice tissues of cancer from patients representing underserved groups (not sure how this will be obtained). • Yes. This project will be of great value to African American and Hispanic men with pancreatic cancer, who have especially poor prognoses. • Pancreatic cancer has a higher incidence in non-Hispanic Black males and females than in all other ethnic groups.
No: 0	*none*

Application #	DISC2-13483
Title (as written by the applicant)	Enabling non-genetic activity-driven maturation of iPSC-derived neurons
Research Objective (as written by the applicant)	We will empower stem cell biologists to generate induced Pluripotent Stem Cell (iPSC)-derived neurons faster and with enhanced maturation by enabling optical cell stimulation and triggering activity-dependent maturation processes
Impact (as written by the applicant)	Our project will address such critical bottlenecks as insufficient maturity of iPSC-derived neurons that limits their utility in age-related neurological disorders that manifest later in life.
Major Proposed Activities (as written by the applicant)	• To fabricate graphene-based substrates for iPSC-derived neurons and human brain cortical organoids in order to use them during subsequent activities for optical cell stimulation • To subject iPSC-derived neurons to repeated patterns of optical stimulation over extended periods of time in order to trigger the electrical activity in neuronal networks • To characterize the changes in functional activity of optically stimulated iPSC-derived neurons that occurred as a result of different optical stimulation protocols • To characterize the impact of the cell activity triggered by optical stimulation on transcriptional and cell population dynamics during activity-dependent maturation • To finalize the validated protocols for light-driven activity-dependent enhanced maturation of iPSC-derived neurons.
Statement of Benefit to California (as written by the applicant)	Neurological disorders are the leading cause of disability and the second leading cause of death. Disease models based on iPSC-neurons allow us to better understand the disease mechanisms and to develop efficacious treatments. However, these neurons often do not exhibit adult-like maturation, limiting the clinical predictiveness of adult disease models. We propose to address this bottleneck by enabling activity-dependent maturation via long-term graphene-based optical stimulation of neurons.
Funds Requested	$675,000
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 90

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

Mean	89
Median	90
Standard Deviation	3
Highest	95
Lowest	84
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	1

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• Neurological diseases are a large class of target indication. • There is an unmet need for methods of maturing neural stem cells in culture for the study of neurological diseases. • In addition, methods for long-term culture of neurons could help researchers perform studies relevant to neurological diseases of aging. • Yes. The proposed graphene-based optical stimulation technology is superior to other methods including electrical field stimulation (EFS) and optogenetics. • The impact of this project could extend beyond neurons to other cell types that can be visually stimulated.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• Yes; the rationale is well conceived. • The applicant has strong preliminary data supporting the hypothesis that their stimulation technology facilitates long-term culture of functional neurons and organoids. • No concerns.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 14	• The need for team expertise in photo-stimulation damage was highlighted in the prior review; this has now been addressed. • The proposed technology optimization studies proposed include clear and justified parameters, metrics, and expected outcomes. • The applicant addressed all comments from the prior review. • No concerns.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 14	• Yes, based on the strength of the preliminary data. • This is a very qualified, well-resourced team. • No concerns.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	• There are race/ethnicity and sex-based disparities within the class of target indications. It would be helpful (next time) if the applicant described these within the proposal. • Yes. The applicant plans to generate functional cortical organoids from ten different iPSC cell lines derived from distinct human genetic backgrounds. The ten organoids will also represents both males and females. • No concerns.
No: 0	*none*

Application #	DISC2-13405
Title (as written by the applicant)	Hematopoietic Stem Cell Gene Therapy for Alpha Thalassemia
Research Objective (as written by the applicant)	The objective of this research is to define the final therapeutic candidate for effective hematopoietic stem cell gene therapy to treat severe alpha thalassemia that requires life-long transfusions
Impact (as written by the applicant)	Severe alpha thalassemia may lead to fetal demise or a life-long need for chronic transfusions with multiple medical complications, especially iron overload from transfusions.
Major Proposed Activities (as written by the applicant)	• Develop lentiviral vectors carrying human alpha-globin gene for gene therapy of alpha thalassemia (AT) and perform initial tests in a cell line. • Test the activities of the vectors in hematopoietic stem cells from healthy donor in culture and by growing in immune deficient mice. • Test the activities of the vectors in hematopoietic stem cells from patients with severe AT in culture that produces red blood cells. • Test the activities of the vectors in a mouse model of alpha-thalassemia. • Determine final therapeutic candidate, complete draft target product profile, and develop assays of purity, activity and identity. • Request INTERACT meeting.
Statement of Benefit to California (as written by the applicant)	AT mutations are most commonly seen in patients of Asian ancestry, particularly South East Asian and Southern Chinese. The prevalence of AT is rapidly growing the United States due to changing immigration patterns. In California, the proportion of the population that is either Asian is 15%, the second highest in the Unites States (behind Hawaii). Thus, patients carrying AT mutations now represent a significant (and ever-growing) public health problem in California.
Funds Requested	$1,323,007
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 90

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

Mean	88
Median	90
Standard Deviation	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/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 15	• Alpha thalassemia (AT) is one of the most common monogenic diseases in the world and a leading cause of significant morbidity and mortality. Furthermore there is a relatively large patient population in CA and Hawaii. Current treatments are limited to allogenic transplants, chronic transfusions and chelation treatments. These treatments are insufficient. The proposed technology could provide a one time cure for AT applicable to all AT patients. • This grant proposes an ex vivo gene therapy treatment for alpha thalassemia, in which a normal alpha globin gene is inserted into autologous hematopoietic stem/progenitor cells (HSPCs) in an attempt to alleviate this hereditary anemia. This could alleviate the need for frequent allogenic transfusions and iron chelation therapy. • Alpha-thalassemia is a major problem. • The proposal is very nicely laid out in a logical progression ultimately leading to an INTERACT meeting with preparation for translation.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 15	• The approach is to use lentivirus to introduce alpha globin by ex vivo gene therapy into patient-specific (autologous) HSCs, then transplant to restore globin balance. This approach has already shown some promise in beta-thalassemia and also sickle cell disease, so this places this proposal on a strong footing. • The scientific rationale is sound. It extends work that has been done for sickle cell and beta thalassemia to AT. • This grant is very focused on achieving a result ready for translation, and it is clear that this has been well-thought out by this group. • This group has good expertise with lentivirus approaches, and seems to be able to modify globin expressing lentivirus vectors to achieve higher titers and increased expression. They also have modified features to increase the expression of globin genes. • The grant contains some good data (Fig. 2) to show that titers and alpha-globin (AG) levels have been optimized over the course of vector/expression cassette design. These have been expressed in cord blood stem cells and they have worked out expression to yield good ratios of alpha to beta-globin expression. • They are proposing a lentiviral approach, which is reasonable. • Preliminary data is adequate. Additional preliminary data on the baseline in vitro "phenotype" on the CD34 cells from the AT patient would be beneficial.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 14	• This grant contains a logical and sophisticated research plan that should yield a candidate approach to treat alpha thalassemias with CD34+ HSPCs that have been retrofitted to express appropriate levels of globins. • This group is expert at globin locus function and have been able to engineer lentiviral expression constructs in which globin gene expression has been optimized. The project plan is logical and sequential, focusing first on lentivirus engineering, then proceeding to testing in HSPCs from normal volunteers, then HSPCs obtained from AT patients. • Logical and well planned study with 6 milestones complementary to each other. • The plan also included mouse studies in an AT mouse model, to show that this approach will work, using human alpha and beta-globin genes for this purpose.

	• Multiple alternative LV vectors are proposed to be evaluated. • Project is well-constructed but the rationale for the milestone testing murine alpha-globin replacement in the mouse AT model is not completely developed. • Pitfalls and relevant toxicity studies could be more robustly described. • Pitfalls and alternatives are not really presented in any detail.
No: 1	• No pitfalls are discussed.
GWG Votes	**Is the proposal feasible?**
Yes: 15	• The proposal is achievable in two years by this group. • The team is excellent. An outstanding team with incomparable experience. It is clear that if there is a team that is capable of constructing a lentivirus construct for AT and bring it to a clinical trial, this is the team. • The team has experience in developing lentivirus-mediated autologous CD34 HSPC products for other diseases and taking them to clinical trial. • The PI and co-workers are experts with globinopathies. • Very strong team. Fairly good progress on a number of related grants; not perfect, but good. • Role of subcontract to an institution is unclear. No letter of support? Concern for significant overlap with an aim of a recently awarded R01.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 15	• Severe forms of AT are prevalent in individuals of South Asian ethnicity, a group that is significant among California residents. This grant is responsive to the need for AT treatment in this group. • AT affects a large proportion of the Asian American population that constitute an underserved population. • The therapy should be generally applicable.
No: 0	*none*

Application #	DISC2-13507
Title (as written by the applicant)	CAR T cells targeting abnormal N-glycans for the treatment of refractory/metastatic solid cancers
Research Objective (as written by the applicant)	Develop genetically modified chimeric antigen receptor (CAR) T cells to kill incurable solid cancers by targeting a previously un-targetable tumor associated carbohydrate antigen.
Impact (as written by the applicant)	Refractory/metastatic solid cancers are almost always incurable and have limited therapeutic options. Directing the immune system to kill cancer cells provides an unprecedented new approach.
Major Proposed Activities (as written by the applicant)	• Engineer and optimize a genetically modified chimeric antigen receptor T cell that targets a tumor associated carbohydrate antigen with high sensitivity and specificity. • Confirm the ability of the engineered CAR T cells to kill diverse solid cancer cells. • Assess the ability of the engineered CAR T cells to kill glioblastoma cells, a highly deadly brain cancer. • Assess the risk of toxicity to normal tissue from the engineered CAR T cells.
Statement of Benefit to California (as written by the applicant)	The citizens of California will benefit from this proposal through development of a new and potent therapy for relapsed/metastatic solid cancers that are incurable and lack effective therapies. The California economy will also benefit from this project through creation and maintenance of bio-tech jobs and the potential to export the therapy worldwide. This project will also further California's international reputation as a global leader in innovation and bio-tech.
Funds Requested	$1,414,800
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 90

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

Mean	88
Median	90
Standard Deviation	4
Highest	90
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/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• The major strength of this project is their novel approach to target tumors utilizing CAR T cells. It is relatively high risk but also high reward . It may extend the target spectrum of cancer immunotherapy beyond traditional antigens to include aberrant carbohydrates as well. This could finally break the barriers solid tumors impose on CAR T therapy. • The branched N-glycans recognized by the lectin domain of L-PHA, included in GlyTR1 CAR T cells and BiTE molecules are ubiquitously expressed antigens found in many tumor types with absent or low expression in normal tissues. • The generation of GlyTR based CAR T cells is a rational next step in the development of agents targeting these antigens and may demonstrate enhanced half-life of GlyTR targeting when compared to the BiTE molecules.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• The preliminary data which has gone through a few cycles of review consistently remains strong and increases our enthusiasm for the rationale. • The movement of CAR T cells to the clinic is well framed. • By targeting a particular antigenic determinant, the proposed approach could be useful in multiple different tumor types. • The rationale for attempting to target ß1,6GlcNAc-branched N-glycans, and the rationale for working on glioblastoma, are both well described, as is the rationale for looking at other types of tumors also. • Two recent studies have demonstrated that the products of MGAT5-mediated and B3GNT2-mediated N-glycosylation inhibit CAR T cell activity. By targeting these antigens with GlyTR CAR T cells, tumor-induced immunosuppression may be reduced or reversed.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 14	• There was no glioblastoma specific data supplied as recommended by the prior reviewers maybe 1 figure on CAR T killing of solid cancer in vitro, so Milestone 3 remains weak and a formal justification beyond being a bad cancer (most of them are!) is not forthcoming. This may be offset by the approach to target solid tumors in general and I am particularly pleased with Milestone 2 and 4. • Regarding the research plan, the orthotopic tumor model for glioblastoma is a strength of this application but I would have liked to see some preliminary evidence that they can generate such a model and what the proposed T cell administration strategy would be? Intraventricular? Systemic? Intratumorally? • The data on their bi-specific protein look quite promising. • The data indicating a greater vulnerability in cancer cells than normal cells is also very promising. • The in vitro work will optimize the CAR design. Substituting residues that will decrease dimerization may reduce tonic signaling and additional lectin domains may increase receptor and cell avidity. The investigators should plan to explore avidity with Lumicks assay. The experimental assays will demonstrate efficacy against multiple cancer histotypes, which was an added plan responsive to prior review. • In vivo studies will evaluate the efficacy of the CAR T cells against cell line derived GBM as well as patient derived GBM. • Tumor model also serves as a toxicology model, given homology in branched N-glycans between humans and mice.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 14	• Have they established a vector that can be translated to the clinic? But this maybe a secondary concern once they reach the IND submission stages.

	• They have optimized the GlyTR1 bi-specific protein, consisting of a sugar-binding domain targeting β1,6 GlcNAc-branched N-glycans fused to a scFv targeting CD3. The GlyTR1 bi-specific protein induces T cell-dependent killing of a wide diversity of solid and liquid cancer cells in vitro and in vivo without killing normal cells or triggering "on-target, off-cancer" toxicity. • What we don't know is whether the proposed approach is going to have any effect on tumor growth in vivo. • The preliminary data in this proposal demonstrated that redirection of T-cells towards the ligands of L-PHA can eliminate tumor cell lines in xenograft models, demonstrating feasibility of the approach. • The investigators have developed CAR T-cells in the preliminary data. Proposed experimental plans are straightforward.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	• It is well known that access to cellular therapies in general can be difficult for underserved communities however this same group as a BiTE molecule in later stages of clinical development. The cancers targeted in this proposal are well known to have poorer outcomes in underserved communities, so I think within the constraints of access to CAR T therapy, they have done everything possible to make this a broadly accessible therapy if successful. • There will be use of cancer cell lines from members of different communities.
No: 1	• CAR T cell therapies do not serve the needs of an underserved community because of the cost of the product and treatment.

Application #	DISC2-13463
Title (as written by the applicant)	Drug Development of Inhibitors of Inflammation Using Human iPSC-Derived Microglia (hiMG)
Research Objective (as written by the applicant)	We will screen for modifiers of the response to misfolded αSyn and Aβ, and their cognate antibodies. Development of drugs to combat this inflammation is important in neurodegenerative diseases.
Impact (as written by the applicant)	Inhibiting the immune response to minimize NLRP3 inflammasome activation may prevent the neurotoxic effect of activated microglia, and attenuate disease progression in neurodegenerative diseases.
Major Proposed Activities (as written by the applicant)	• High-throughput Screening: Screen for hit-to-lead compounds that inhibit immune activation triggered by misfolded proteins, monitored by (1) IL-1β reporter line and by (2) ELISA (month 1 - month 6). • Efficacy Evaluation of Hits: Evaluate candidate therapeutics in hiMG using misfolded proteins in the presence and absence of their cognate antibodies (month 6 - month 18). • Drug Optimization (month 18 - month 24). • Further Develop and Complete A Target Product Profile (month 21 - month 24).
Statement of Benefit to California (as written by the applicant)	This proposal will benefit citizens of California by developing new treatments for Alzheimer's disease and Parkinson's disease based on new anti-inflammatory pathways studied in the innate immune cells of the human brain, represented by hiPSC-derived microglia. These diseases are very prevalent in California, and cause both personal tragedy to families and undue economic burden. Developing a new therapy for these conditions will alleviate this suffering while benefitting the California economy.
Funds Requested	$1,658,123
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 90

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

Mean	88
Median	90
Standard Deviation	5
Highest	94
Lowest	80
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	11
(1-84): Not recommended for funding	3

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 13	• There is an urgent need for more effective Alzheimer's disease (AD) treatment. • The proposal has high potential for identification of a treatment for AD and potentially other neurodegenerative disorders. • Nrf2 as a known and interesting target. • AD has huge morbidity and mortality. The need is so immense - it's important and worthwhile to take more "long shots" on this topic than, say, for a very rare disease. • The bar for pursuing a novel AD therapeutic should be very low. No current medications work better than lifestyle modifications. So although it is unlikely that the proposal will result in a "gamechanger," even a small potential benefit is worth CIRM's investment. • Even if the medication has a small translational impact, it could also light the way for future medications. Carnosic acid derivatives target specific aspects of a complex pathophysiology. Therefore, they may only work in some people, or only in combination with other therapies. This would increase the flexibility of front-line therapeutic options. • Success here may inspire others. • There are no other candidate drugs for AD that target this specific pathway. Some weak evidence exists that anti-inflammatory medications (e.g., aspirin) may have some value in preventing or treating dementia. Molecular understanding of their mechanism(s) of action is lacking. • As mentioned in the prior review, the application has limited discussion about why investigators will not screen larger compound libraries (instead of focusing on phenols).
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• The applicant provides a clear rationale for using group of molecules as a starting point for therapeutic discovery, along with solid preliminary data. • Some scientists are reluctant to endorse an approach to AD that does not seek a "silver bullet" targeting an AD-specific molecular mechanism. This conceptualization of AD was popular decades ago, and may remain in the minds of many scientists that specialize in diseases other than AD. Modern approaches in the field tend to embrace multimodal causation and multimodal therapies for AD. • There are two reasonable pathways by which carnosic acid derived compounds might be therapeutically useful. One is direct, and could apply to all or most patients with misfolded protein aggregates that potentiate dementia, AD, or neurodegeneration. The other approach would be the use of such a compound as an adjuvant for an antibody therapy. • Yes; aging is known to impact the phagocytic capacity of microglia, which seems to contribute to pathology in AD. One concern is that the applicant will use normal microglia for drug screening, rather than microglia from AD patients. • Previous efforts to reduce inflammation in humans have been attributed to limited access to the brain and inadequate distribution to relevant regions. There are no preliminary data provided that address this bottleneck. • Yes. Inflammation is very relevant in AD.
No: 1	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 13	• The applicant has sound methods to identify therapeutic compounds. • The proposal is extremely well-designed. I have no concerns. • Overall, yes. Perhaps more clarity about the range (upside to downside) of the number of compounds likely to be present in each step would belong in such a section. • This project follows standard protocols for target optimization. No great leaps or miracles are required for success. • Although I would have preferred to see more of diversity of controls (e.g., other anti-inflammatory drugs), these controls are adequate.
No: 0	*none*

GWG Votes	Is the proposal feasible?
Yes: 12	• No major concerns. • Based on the expertise of the team and the significant amount of data provided on the application, I have no doubt the project is feasible. • Yes. These applicants have considerable experience in screening compound libraries for new drugs and bringing them to market. Notably, the Principal Investigator was largely responsible for bringing memantine to market, which is one of the few drugs for AD that is standard of care. • The applicants have previously received CIRM funding for grants that used some of the same techniques and have performed well on these grants. • The institution is a very strong environment for drug development and this kind of research.
No: 1	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	• The costs associated with treatment using a drug (versus a cell therapy, for example) are much lower. Therefore, underserved communities can be more easily served. However, one potential problem is that patents can be used to limit the drug's benefits to the affluent. • The best way to support underserved communities is to create low cost interventions. A small molecule should ultimately cost less than gene therapy or antibody therapies. • A diverse array of iPSCs are used, in the unlikely event that they respond differently to the small molecule. Given the mechanism of action, it is unlikely that MHC-locus plays much of a role.
No: 0	*none*

Application #	DISC2-13390
Title (as written by the applicant)	Cardiac Reprogramming Gene Therapy for Post-Myocardial Infarction Heart Failure
Research Objective (as written by the applicant)	The candidate is a gene therapy that delivers cardiac reprogramming factors to convert resident cardiac fibroblasts into functioning cardiac muscle. Thus, it is a regenerative cardiac gene therapy.
Impact (as written by the applicant)	The targeted condition is heart failure arising from myocardial infarction or other insults causing focal heart muscle loss. Cardiac muscle cells are post-mitotic and unable to renew after injury.
Major Proposed Activities (as written by the applicant)	• Complete test article manufacturing to support large animal efficacy study • Select a development candidate based on results of large animal efficacy study comparing two lead candidates
Statement of Benefit to California (as written by the applicant)	Heart disease is a leading cause of death in adults and children in California, but there is no current treatment that can promote cardiac regeneration. This research will benefit the state of California by laying the groundwork for development of a one-time treatment that could correct heart disease by generating new heart muscle cells from within the heart. If successful, there is potential economic benefit in terms of productive lives saved and in commercialization of this technology.
Funds Requested	$1,215,000
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 88
Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	88
Median	88
Standard Deviation	1
Highest	90
Lowest	85
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 13	• Treatment of cardiovascular disease is indeed an unmet medical need. The proposed technology from this proposal is not a stem cell technology, it is focused on gene therapy. Based on the research plan, they are trying to scale up virus production. • The technology addresses the unmet need of cardiac muscle regeneration in patients with heart failure with reduced ejection fraction. Cardiomyocytes lack regenerative capacity so patients with this disease suffer chronic reduced cardiac function. • There are no treatments for repairing the heart after myocardial infarction. • This project plans to treat cardiovascular disease using cellular reprogramming approach. They identified a combination of two genes for converting human cardiac fibroblasts into cardiomyocytes (CM). • The technology represents a gene therapy to convert cardiac fibrobasts to cardiomyocytes. If effective, this has the potential to provide an effective new treatment for heart failure. • Significant preliminary work has been done in rodent models. This proposal will test viral delivery of reprogramming factors in a more clinically-relevant large animal model. This represents a logical next step in translation and will provide key information guiding design of human clinical trials.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• Reprogramming cardiac fibroblasts into cardiomyocytes is a sound regenerative strategy to increase the number of CMs in heart failure patients. • Cardiac reprogramming based on transcription factor overexpression is scientifically correct. • The preliminary data and methodology to reprogram cardiac fibroblasts to cardiomyocytes is the key strength to this technology. • The applicant provided preliminary data in human cardiac fibroblasts and in a rat chronic myocardial infarction model. Therefore, their data is compelling and supportive. • Preliminary data demonstrate conversion of cardiac fibroblasts into cardiomyocytes in a rat model, and resulting improvements in cardiac function. • The rationale is high risk. In addition to general safety concerns with viral gene therapy, specificity of conversion is important. The extent of cardiac fibroblasts conversion to CMs is also important; too many CMs would be problematic. Appropriate tissue organization is also important to survival and function. These are difficult processes to control. • A preliminary large animal experiment demonstrates proof-of-concept in this model.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 13	• Yes. They will scale up their virus production and then test in large animals. • This is a very simple study design that compares two different virus capsids for CF infectivity and tropism. • The manufacturing plan is clear and quality control is comprehensive. • The endpoint analysis of >10% improvement in left ventricular ejection fraction is appropriate. • Biodistribution and safety considerations are well-designed. • The studies are well thought out. The repeat study of the candidate de-risks the proposal and will establish if the catheter deployment of plasmid via injection yields similar results to the earlier open heart injection procedure. • The major weakness of this model is the lack of the ability to determine mechanism of action via kinetics and extent of reprogramming.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 13	• Timeline is reasonable. • Milestones for manufacturing and performance in the large animal model are logical and appropriate.

	• The team has expertise in virus manufacturing and in cardiac fibroblast reprogramming to cardiomyocytes. • The collaborating team has expertise with the large animal model. • The preliminary data suggests that all aspects of the study can be performed.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	• Heart disease affects all communities in the diverse California population and is overrepresented in some underserved racial and ethnic communities. Development of this technology could have a major impact on the unmet medical needs associated with heart failure. • The proposal will use both male and female large animal models, and notes that estrogen affects response to the myocardial infarction model. • Myocardial infarction affects the general population including diverse individuals.
No: 0	*none*

Application #	DISC2-13417
Title (as written by the applicant)	AAV-dCas9 Viral Epigenetic Editing for CDKL5 Deficiency Disorder
Research Objective (as written by the applicant)	We propose a gene therapy for the treatment of a severe infantile epilepsy called CDKL5 Deficiency Disorder using CRISPR-mediated epigenetic editing
Impact (as written by the applicant)	A transformative treatment for females affected by CDKL5 Deficiency Disorder in addition a platform for the approximately thirty-eight other X-linked intellectual disabilities that predominately affect females
Major Proposed Activities (as written by the applicant)	• Validation of CRISPR editing (CRISPRe) in CDKL5 Deficiency Disorder (CDD) human neuronal cell models • Safety and Off-Target profile of CRISPRe in CDD human neuronal cell models • Rescue of behavioral and functional outcome measures in two mouse models of CDD following CRISPRe administration • Molecular and Histological Characterization following CRISPRe administration in two mouse models of CDD • Safety of CRISPRe in two mouse models of CDD
Statement of Benefit to California (as written by the applicant)	CDKL5 Deficiency Disorder (CDD) occurs in 1 of 40,000 live births meaning there are ten CDD patients born in California each year. CDD has a drastic impact on the quality of life for both the patient and caregiver. Over 43,000 people in California have an intellectual disability. A high number of causative genes for intellectual disabilities are found on the X chromosome. This grant will not only develop a treatment for CDD but may provide a roadmap to treat other X linked disorders.
Funds Requested	$1,429,378
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 88

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

Mean	88
Median	88
Standard Deviation	2
Highest	90
Lowest	83
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	1

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 13	• CDKL5 Deficiency Disorder (CDD) is a rare X-linked dominant genetic condition which results in early onset, medication resistant seizures, and severe neurodevelopmental impairment. Currently there are no approved drug or gene therapy treatments for CDD. This project will provide a new strategy for treating CDD. • This project will help accelerate the likelihood of developing a new method for treating CDD. • Yes. Per their proposal, the applicant will test their gene editing approach for off-target effects in human neurons. They propose to use animal models to study whether CRISPRe can rescue behavioral phenotypes of CDD. • Yes. The applicant's technology addresses an epileptic encephalopathy for which there is no current treatment. The approach should be applicable to other X-linked genetic disorders. • The proposal outlines the applicant's future plans for a phase 1 trial. Appropriate collaborations for the trial are in place. • The proposed therapeutic approach would reactivate the healthy CDKL5 gene and likely to provide lifelong benefit from a single intervention. This has the potential address the unmet need for CDD.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• CDD is a rare epileptic encephalopathy caused by mutations in the CDKL5 gene, which lies on the X chromosome. Due to the random X chromosome inactivation that occurs throughout all cells in the female body, females with mutations in one copy of the CDD gene express that mutant copy in some, but not all, cells. Therefore, broad silencing of the mutant copy with parallel reactivation of the healthy copy is a rational approach. • This proposal is technically sound. In the applicant's approach, the mutated copy of CDKL5 is silenced and the healthy (normal) copy is activated. • Yes. Reactivation of the healthy (normal) copy of CDKL5 on the inactive X chromosome by epigenetic targeting is a valid approach. • Is it clear that gene editing by removal of DNA methylation marks will result in reactivation in vivo? Activation as shown in a cell model (Figure 7F) appears variable. • Preliminary data show that the applicant's CRISPR activation system works in situ in mouse neurons. • Product testing in patient iPSC-derived neurons as a disease model would be helpful.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 13	• This project is well planned. The applicant will first test their CRISPRe activation system in vitro and then move to mouse model studies. • Plans include thorough assessment of potential efficacy and safety in human cells (in vitro) and mice (in vivo). • Success of the project will require delivering a complex payload via AAV. However, preliminary data suggest this will work. • The project will benefit from strong phenotyping capability in vitro and in vivo. • The proposal doesn't mention that the X chromosome can erode in cell lines. This is a limitation to interpretation of in situ findings that should be addressed. • Potential off-target effects are considered thoroughly. • The project is well-planned and well-designed overall. Ultimately, the applicant plans to enroll female participants with CDD from ages 1 to 15 in a phase I clinical trial. One concern is whether the proposed preclinical mouse models (at 21 days of age) are representative of the human condition, particularly brain development.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**

Yes: 13	• The proposed milestones are logical. However, I am concerned that the applicant may not be able to finish all the experiments in two years. The animal experiments will be particularly time-consuming. • The team has appropriate experience and provides strong preliminary data. • The project is to evaluate the efficacy and safety of the identified therapeutic candidate in pre-clinical mouse models. The proposed milestones are likely to be achieved if no complications arise.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	• Yes, CDD primarily affects a small population of females. • Females are predominantly affected by this condition. • The proposed therapy would benefit all females affected by CDD, regardless of the specific disease-causing mutation.
No: 0	*none*

Application #	DISC2-13415
Title (as written by the applicant)	Defining the Optimal Gene Therapy Approach of Human Hematopoietic Stem Cells for the Treatment of Dedicator of Cytokinesis 8 (DOCK8) Deficiency
Research Objective (as written by the applicant)	A new therapeutic option for DOCK8 deficiency using autologous human hematopoietic stem cells modified through either lentiviral gene addition or CRISPR/Cas9 based gene editing.
Impact (as written by the applicant)	Allogeneic HSCT is complicated by comorbidities that can be addressed by autologous stem cell gene therapy. This is relevant for DOCK8 deficiency and can be applied broadly to other genetic diseases.
Major Proposed Activities (as written by the applicant)	• Develop an optimized lentiviral vector gene therapy approach of autologous hematopoietic stem cells for the treatment of DOCK8 deficiency. • Design a site-specific CRISPR/Cas9-mediated gene editing approach for DOCK8 deficiency. • Compare the effects of the DOCK8 lentiviral vector gene addition and CRISPR/Cas9 gene editing on hematopoietic stem and progenitor cell survival. • Assess the repopulating capacity of gene-modified hematopoietic stem and progenitor cells through transplantation into immunodeficient mice. • Finalize the therapeutic candidate to advance to the next stage of development and initiate assays to characterize the Drug Product. • Assemble an INTERACT Meeting Package for submission to the FDA to request a consultation to discuss the therapeutic candidate.
Statement of Benefit to California (as written by the applicant)	Safe, definitive therapies for DOCK8 deficiency represent an unmet medical need. Allogeneic stem cell transplant is frequently complicated by graft-versus-host disease and worsening of pre-existing infections. Demonstration that autologous stem cell gene therapy can safely and effectively cure DOCK8 deficiency will shift the paradigm by which patients will be treated, led by California's position as a leader in the field of gene therapy.
Funds Requested	$1,386,232
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 85

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

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

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 13	• This proposal could yield a novel approach to treat DOCK8 deficiency, which currently does not have good treatments. • The approach is straightforward--to engineer CD34+ hematopoietic stem cells (HSCs) obtained from patients to contain a construct that restores DOCK8, then use these as a source of autologous grafts to restore a functional immune system. • This treatment would alleviate the need for use of antibiotics and immunoglobulin infusions. In addition, this would be better than allogenic HSC grafts that are now used. • The proposed work will test two modalities to rescue patients with DOCK8 mutations. • The PI provides preliminary evidence in support of the main approach, which is to use lentiviral re-expression of DOCK8 or directly correct DOCK8 gene loci via CRISPR/Cas9 targeting of hematopoietic stem cells from DOCK8 immunodeficiency syndrome (DIDS) patients. • If these new therapeutic candidates are shown to be successful as per the proposed work, then there is a high degree of likelihood that these findings will lead to new stem cell-based therapies to improve patient care. • Its exact prevalence is unknown given the high likelihood of under-diagnosis, but it is currently estimated to occur in less than one in one million individuals. There is a need to know how frequent/prevalent DOCK8 mutations are, and the likelihood of being able to recruit sufficient participants for an eventual clinical trial. Applicants state there is a risk there may not be patients who are able to donate HPSC for the project plan, so there may be a risk of not finding participants in an eventual trial.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• Since DOCK8 immunodeficiency can be treated with allogenic HSC engraftment, the likelihood that autologous HSC grafts (corrected for DOCK8) will work is high. This approach would also likely eliminate risk of graft versus host disease. • The applicant has already expressed the cDNA in cells with lentivirus and shown good expression. DOCK8 function has also been demonstrated. • The main rationale for the work is solidly based on pre-clinical results showing the expression of the DOCK8 transcript using lentiviral delivery systems. • The successful use of a lentiviral construct is significant given the size of the DOCK8 transcript. • The gene therapy approach is sound.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 12	• This grant will likely yield an approach for the treatment of DOCK8 deficiency using an autologous ex vivo gene replacement strategy in patient-derived autologous HSCs. At the conclusion, this project should be ready for translation. • The use of optimized DOCK8 cDNA is a good design feature. • Though the grant does not contain specific pitfalls and alternative sections, the discussion in the research plan suggests that the PI appreciates the complexities associated with expression of a large cDNA. • The proposed work is outlined as 6 milestones. The first is focused on generating an optimal lentiviral construct to express DOCK8, to establish vector production methods and

	transduction conditions to restore DOCK8 expression. This aim extends work currently funded by CIRM to produce a lentivirus encoding DOCK8. • Milestone 2 will make use of CRISPR/Cas9 targeting to insert corrective cDNA constructs. Additionally, the target site will be used as a potential safe-harbor location for the expression of the corrective cDNA. Of note, sgRNA have been optimized for low off-target effects. • One pitfall of not directly repairing the DOCK8 gene is that the mutant version of DOCK8 may act as dominant negative form, disabling the transgenic expression of the wildtype DOCK8 version. However, the more challenging double inserting correction may overcome this problem by interfering with the expression of the endogenous mutant version of the gene. • Milestone 3 will test human HSPCs modified either by lentiviral or CRISPR/Cas9 additions to undergo differentiation in vitro. It is unclear what the expected results are from this analysis, other than test whether modified cells can be placed in vitro to undergo differentiation. • Milestone 4 is similar to #3 but will take the gene modified CD34+ cells and transplant them into neonatal mice. The key aspect is to determine the frequency of gene modified cells present in the mice several weeks after engraftment. • A key aspect of Milestone 4 is the adoptive transfer of gene modified human CD34+ cells that are obtained from DOCK8 patients. This serves an excellent test of the main hypothesis and validation of the therapeutic potential. • Milestones 5 and 6 will prepare for next translational steps of the therapeutic approach. Given the uncertainty of the candidate approach, these milestones are not well-justified.
No: 1	• "In addition, biostatisticians are available in multiple departments throughout [the institution], one of whom has performed statistically analyses for [the PI's] other projects and has familiarity with projects on gene editing." This very vague statement does not add confidence that the applicants will be able to do adequate statistics. The saving grace here is that a biostatistician is not needed here. The application would have been stronger if they had just left out the comment.
GWG Votes	**Is the proposal feasible?**
Yes: 13	• No concerns. Seems very feasible. • Yes, the proposed aims are well structured and feasible within the outlined timeframe. • The proposed work is well structured and of high quality. There is a high degree of innovation and elegance in the proposed work. Nonetheless, there are some concerns as to the feasibility of whether all approaches will lead to a successful rescue of DOCK8 function. • Related award progress is pretty good, but not perfect.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	• DOCK8 deficiency is a very rare genetic disease, one out of a million. It seems this treatment could be made available to individuals regardless of ethnicity, though there is probably under-diagnosis in underserved communities. • This is a very rare disease, nonetheless, the PI points out and addresses these factors in the proposal. • This gene therapy should be broadly applicable.
No: 0	*none*

Application #	DISC2-13498
Title (as written by the applicant)	Bioengineering human stem cell-derived beta cell organoids to monitor cell health in real time and improve therapeutic outcomes in patients
Research Objective (as written by the applicant)	We will generate nanoprobe-containing stem cell-derived human beta cells that can be monitored in real time in response to inflammatory stress upon transplantation in patients with type 1 diabetes.
Impact (as written by the applicant)	Our product will replace donor islets for cell replacement therapy in patients with type 1 diabetes, and will provide a readout of cell survival and an opportunity for therapeutic intervention.
Major Proposed Activities (as written by the applicant)	• Test insulin-producing cell organoids with nanosensors to secrete insulin in response to elevated glucose and emit a signal in real time, and test similar activities in animal models of diabetes. • Test the ability of insulin-producing cell organoids with nanosensors to emit a measurable signal in response to increased inflammation in vitro and after transplantation in small animal models
Statement of Benefit to California (as written by the applicant)	The American Diabetes Association states that California, with the highest number of patients with diabetes in the country, also has the highest cost at $39.47 billion. A large proportion of these patients are insulin-dependent and are potential candidates for islet replacement therapy. Developing technologies that can improve transplantation outcomes in patients directly affects long-term quality of life.
Funds Requested	$1,198,550
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 85

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

Mean	85
Median	85
Standard Deviation	2
Highest	87
Lowest	80
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	11
(1-84): Not recommended for funding	4

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 15	• The proposed technology is designed to generate allogeneic hiPSC-derived insulin-producing organoids containing nanosensors to allow non-invasive graft monitoring after transplantation. This technology could allow the rescue of compromised grafts therefore increasing the number of people that could benefit from the treatment. If successful, the applicant will team up with biotech/pharma developing hPSC-derived islets to deploy their nanosensor technology for beta cell replacement strategy. • This is a very innovative technology that will implement future stem cell-based therapies. It might not accelerate deployment of such therapies, but it could be part of the next generation product. • This product could aid the design of enhanced beta cell replacement therapies or other stem cell-based therapies in preclinical studies, by identifying the ideal site/combination product for successful engraftment and functionality. • The nanosensors developed by the applicant are innovative and have the potential to advance monitoring of implanted cells and tissues to advance numerous regenerative therapies. • There remain some concerns about the depth of penetration of optical monitoring. This revised proposal better addresses this concern but the applications and implantation sites will be limited. • The ability to enable interventions in patient care following cell therapies is new and innovative. This has the potential to significantly improve the outcome of stem cell-based therapies • The focus on development in vitro and in the mouse model is appropriate early stage translational research. The revised project better considers eventual translation to larger animals and the challenges associated with this. • The eventual interventions that might be undertaken upon immune stress are not discussed. While information about immune stress is likely useful, it isn't clear how this will advance outcomes in patients. • Addresses an important problem • Exciting tool • It will provide a tool for assessment of local inflammatory response of implanted cells that can be assessed non-invasively.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 15	• The proposed project is based on sound scientific rationale, as being able to assess the viability of the graft in real-time could provide a window of opportunity to rescue graft function. It is however, unclear what type of intervention could be applied to rescue graft function should the graft become compromised and how would they know if the treatment worked if the signal is irreversible. • The team has strong preliminary data showing Raman signal detection from mice transplanted with cells (not sure if cadaveric human islets or INS1) 2 days post-transplantation under the kidney capsule. • With a collaborator, gold nanoparticles were introduced into hPSCs which were then differentiated to insulin-producing cells using an INS-GFP reporter cell line, gold particles were detected in the cytoplasm of cells at the end of the differentiation • The preliminary data is strong and the proposal well-designed but given that the proposal rests heavily on signal detection in the kidney, I would have liked to see that they can indeed detect a signal from hESC-derived kidney grafts (they must have the data from the transplants in fig 7). • The team detects similar levels of c-peptide from mice transplanted with hESC-derived islet cells with or without nanoprobes, suggesting nanoprobes do not interfere with c-peptide secretion. • The use of beta-cell containing organoids to treat T1D is sound. There have been significant studies demonstrating the ability to control glucose in small animal models using this technology. • The use of nanoparticle sensors to monitor miRNA as a way to assess cell state in vivo is innovative. Significant proof-of-concept is provided to establish confidence in this technology.

	• Significant work has been done in developing nanosensing technologies for use in living cells in vitro and in vivo. Since the prior submission this technology has been demonstrated in the iPSC-derived spheroids. • Much more focused, potential broad impact. • The technology for probe development as a tool is sound. The application to humans maybe limited by depth of optical penetration for sensing.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 15	• The project is designed to meet the expected outcome and develop an add-on (nanoprobes) that will advance beta cell replacement therapies. • The project is clearly structured to further develop the nanosensor technology using on "ON" sensor to optimize sensing of cells in vivo, then to extend this technology to incorporate probes that detect inflammation through miR146a • The focus on inflammation sensing in the mouse model is appropriate for early stage translation. Use of multiple implantation sites and other tissue structures (e.g. large animal skin) could help advance to next stage model systems. • A linkage between miR146a sensing and cell/spheroid viability and function has not yet been established. It's unclear how the information gathered by this sensor technology will be used in a translational therapy at this stage of development. • The use of in vitro models to accelerate sensor development then validation in vivo is clearly justified. • Experiments are well designed with clear goals, comparison groups including controls, and analytic techniques. Statistical considerations are clear. A focus on both molecular characterization of cells as well as cell viability and potency will be related to nanoprobe signal. • The team proposed ways to induce inflammatory stress and monitor probe signals and implant outcomes. • There is risk that the inflammation signals will not directly inform on implant health, especially given the irreversibility of the probes. However, the experiment design will answer this question. • Translation to human not clear. • Therapeutic strategy not clear. • The plan is logical and in vitro and in vivo data showing C-peptide secretion by cells with and without the probe is critical.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 15	• The experimental design is well-constructed and feasible. • The quantitative milestones and detailed success criteria are a strength of the project. • The company has expertise in iPSC differentiation, nanoparticle sensing, and the animal model. They are well-equipped to complete the proposed study. • The preliminary data is strong and demonstrates proof of principle.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 15	• The applicant makes a good case for beta cell replacement therapies addressing the need of the undeserved communities, if made accessible to all. • The project will use iPSC lines that are derived from diverse donors. • The mouse model does not account for differences in sex. • Diabetes disproportionately affects underserved communities so the proposed technology has the potential to impact unmet needs in these communities. • The applicant has strong connections to racial and ethnic minority communities in California • Diabetes and local inflammation of implanted cells affects the general population.
No: 0	*none*

Application #	DISC2-13469
Title (as written by the applicant)	Novel antisense therapy to treat genetic forms of neurodevelopmental disease.
Research Objective (as written by the applicant)	We propose to discovery and evaluate antisense gene therapy for specific mutations underlying debilitating or life-threatening neurodevelopmental diseases including epilepsy and autism syndromes.
Impact (as written by the applicant)	The conditions are four specific neurodevelopmental syndromes where mutations are well-suited to antisense oligonucleotide (ASO) therapy. The bottlenecks are current lack of cellular evidence for ASOs to impact disease course.
Major Proposed Activities (as written by the applicant)	• Assemble a cohort of patients and their stem cells for study where personalized ASOs could be reasonably expected to reverse the effect of genetic mutation and lead to clinical improvement. • Identify evidence of baseline cellular defects and gene expression defects in patient-derived stem cells from this cohort of patients. • Design ASOs for each mutation that can correct the genetic mutation in collaboration with a foundation. • Assess ASO therapy for effectiveness and safety, and compare with control healthy stem cell lines. • Deliver outcome data from this study to the PI in support of future FDA applications.
Statement of Benefit to California (as written by the applicant)	Neurodevelopmental disease impacts 1:50 Californians with conditions like severe epilepsy and autism. In prior CIRM-funded efforts we generated a library of stem cells from patients, and in parallel we identified their genetic mutations. Now the stage is set to test if correction of the genetic mutation through ASO gene therapy can show evidence of disease-modifying activity in patient cells. Results will support future clinical trials where these drugs will be administered to patients.
Funds Requested	$1,180,654
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 85

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

Mean	85
Median	85
Standard Deviation	2
Highest	90
Lowest	80
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	10
(1-84): Not recommended for funding	3

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 12	• The applicants will, in collaboration with a foundation, develop an antisense oligonucleotide (ASOs) gene therapy for initially four different single-gene neurodevelopmental disorders (NDDs). The aspect of this project is to test relevant target engagement and efficiency in relevant patient-derived stems. • The need for such a project is very high due to the nature of the disease. • This is a well-constructed, well-written and a high quality project proposal, backed up by an experienced team with relevant expertise. The proposed technology is likely to result in a candidate, a novel antisense gene therapy, for treatment of rare genetic form(s) of neurodevelopmental disorder(s), for which at present, there are no effective treatments and therefore they constitute a high unmet medical need. • In addition to developing a new candidate treatment, this project also proposes to explore cellular dysfunctions in patients' cells, which is another unmet need. Many disease-related phenotypes are not yet known and are the major impediment for development of novel therapies. • Although translation is not part of this proposal, the applicants have presented a well thought-through path for progression from a successful candidate to patients. Thus, they propose testing of selected candidates based on their in vitro work and in vivo in rodent models for toxicity before moving to the clinic. • This is an exploratory project that has potential. • This project has a potential fast track to human application. There are already other ASO therapies in clinical trials and a special pathway to the clinic is provided by the FDA for such therapies.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• The proposed project is based on a very sound scientific rationale and uses approaches previously successfully used in clinical practice. The choice of the selected four selected genetic mutations/diseases is well argued. • The revised proposal provides more clear rationale than the first submission. • The rationale is straightforward and the applicant has addressed previous questions and concerns. The establishment of efficacy and performance in patient-derived neural precursor cells (NPCs) with specific ASOs seems a necessary and first step in this process. • The applicant has access to patient relevant hiPSC lines to generate NPC from two different patients for four monogenetic diseases. They will use additional lines from 8 healthy individuals for comparisons. While this seems overambitious, the pipeline approach the applicants have generated will be suitable to handle this many cell lines. • The milestones should be achievable as the applicant has already a considerable amount of sequencing information. In addition, the applicant will work with the foundation to generate the candidate ASO drugs, delivered to the lab for this project. This step is further supported by the foundation connections with another partner, who had additional capacities.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 11	• The proposed project is well planned and designed from the experimental and technical point of view. The project is likely to meet the expected outcomes and identify a candidate (or more) to advance to translation.

	• Efficiency study on knockdown efficiency suggests successful knockdown. The applicant identified at least 3 ASOs with >20-fold specificity for the mutant haplotype that generates a toxic GoF mutation in SCN2A. These ASOs are currently in safety studies. They now want to use the same approach for the other diseases outlined in the application. • Data to support Aim 2 are strong. • The project is overall sound. The PI proposes the use of isogenic controls for each patient-specific iPSC line. It sounds like readout will be based solely on RNA-Seq and western blot (no functional studies). If the whole project is in vitro, only two iPSC lines per mutation may not be sufficient. • Major concern here is that, although well planned and designed for dealing with one disease at a time, there may not be enough time to provide good quality work on 4 different diseases, which ultimately, may reduce the chances (not increase as the applicants suggest) of developing a successful candidate. • It is unclear what may realistically be expected due to the sheer number of possible cellular phenotypes the applicants propose to explore, combined with the lack of previous data. • There are no data provided as to the endpoint analysis in the cells. The applicant refers to a manuscript that uses a mouse model and none of the proposed assays are described in this reference.
No: 1	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 12	• This is a well-planned project and the milestones and expected outcomes are very logical. However, reducing number of investigated NDDs (e.g. from 4 to 2) and increasing the number of involved staff would be beneficial to ensure that all the deliverables are achieved in a timely manner. However, given the expertise of the applicants and the involvement of the foundation, they have a high potential of reaching all the proposed milestones. • Importantly, the team had already developed some necessary resources as part of their previous CIRM-funded project, and is backed up by further resources via the foundation. • The connection to the foundation is of particular value. • I believe it is feasible based on the PI and collaborators. However, the proposal does not provide sufficient preliminary results to indicate feasibility. Some of proposed experiments are vague so it is hard to anticipate feasibility and how results will be interpreted. • The team is highly qualified in most aspects of the application and the PI has extensive experience in animals models and ASO approach of NDD. Expertise in the in vitro analysis of the endpoints in the derived neurons and organoids is less apparent and should have been addressed more clearly. • The applicant assumes that the single mutations will show the expected readout in NPC and will impact measurements of growth, death, morphology, cytoskeleton, trafficking, and assess specific signaling, post-translational protein modification, and synapse morphology and excitability as predicted from gene function. This assumption is not supported by any data nor are any endpoint measures shown in preliminary data
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 12	• The applicants have provided detailed descriptions and rationales related to this, taking into account the geographical area and its population. • The proposed approach is sound, and the potential product/treatment will serve the unmet medical needs of diverse and undeserved communities. • One remarkable aspect of the project that, if successful, will provide a life-long therapy free of cost. This is possible due to the involvement of a non-profit organization that will carry a significant amount of costs and provide additional funding.
No: 0	*none*

Application #	DISC2-13428
Title (as written by the applicant)	Therapeutics to overcome the differentiation roadblock in Myelodysplastic Syndrome (MDS)
Research Objective (as written by the applicant)	This proposal will deliver a small molecule therapeutic candidate for the treatment of Myelodysplastic Syndrome (MDS) and will act by inducing differentiation on mutated hematopoietic stem cells (HSCs).
Impact (as written by the applicant)	This application will enable development of a therapeutic candidate for the treatment of MDS, a preneoplastic hematological condition of HSCs.
Major Proposed Activities (as written by the applicant)	• Determine the Myelodysplastic Syndrome (MDS) subtypes and mutational signatures responsive to differentiation induced by the lead series (Q1-Q2, YEAR 1). • Establish in vivo proof of concept differentiation with oral compound administration (Q1-Q2, YEAR 1). • Establish an ideal preclinical candidate with requisite pharmacology, safety, and efficacy (Q1-Q8, YEARS 1-2). • Further define the mechanism by which the lead series promotes differentiation in MDS (Q1-Q6; YEAR 1-2).
Statement of Benefit to California (as written by the applicant)	This work will generate a novel therapeutic candidate for the treatment of Myelodysplastic Syndromes (MDS), a life threatening hematological condition that is rapidly becoming more common as our population ages. In contrast to bone marrow transplants, which are at present the only curative treatment for MDS, this application will deliver a more equitable small molecule therapy with greater access for underserved communities, for whom the risk factors for developing MDS are more common.
Funds Requested	$1,244,160
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 85

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

Mean	84
Median	85
Standard Deviation	4
Highest	87
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	2

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• The outcome of a successful project here could be highly impactful to a large number of Myelodysplastic Syndrome (MDS) patients who have no real effective treatments. So I have no problems with the rationale, significance and I am most enthusiastic about the success of this project after reviewing their preliminary data. • Intriguing treatment for MDS. Inhibiting heme in undifferentiated cells is a novel approach. Learning more about this therapeutic approach opens a new door towards MDS therapy.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• I am mildly concerned that Aims 2 and 3 are dependent on Aim 1 which in turn is simply an expansion of their completed prelim work but convincing statistics for success are not provided (arbitrarily picking 20 MDS samples to study). Since I am quite convinced with their prelim data, I am fairly confident that Aim 1 and therefore 2 and 3 would be completed despite being dependent on each other. • "Unlike previous reports, we observe cellular potencies in MDS cells" needs a citation. What did the previous reports observe in MDS cells? • "We note that while differentiation therapy has been proposed as a therapeutic paradigm before," needs a citation.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 12	• MDS is a new area of research for this team. In some ways I am glad they have channeled their efforts to target a horrible disease with minimal curative options, but also leaves them inexperienced to work with MDS cell lines, patient and mouse models. They do have strong collaborations and so far have demonstrated that they can complete at least in vitro assays. I would be reserved about the mouse models in Aim 2- they may lean on collaborators considerably • No pitfalls are mentioned. One alternative approach is mentioned for biomarker discovery • Figure4A is blank.
No: 2	• Inadequate design.
GWG Votes	**Is the proposal feasible?**
Yes: 14	• I am skeptical of the applicant's ability to implement sample sharing (required in Aim 1) within 60 days of notice of award. • Perhaps if a materials transfer agreement (MTA) is needed to enable this research, CIRM could make acquisition of that MTA as a milestone.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 14	• I think their major strength here is that they have thought of adapting this therapy as an oral agent which is more likely to reach most patients in need compared wtih a cell therapy like allogeneic transplant. I also think the have some strengths in collaborating with large biobanks with diverse samples to work with. • Small molecules may ultimately be less expensive than other therapies, so this might be a good option for economically disadvantaged patients.
No: 0	*none*

Application #	DISC2-13456
Title (as written by the applicant)	Novel methods to eliminate cancer stem cells
Research Objective (as written by the applicant)	Our goal is to develop and optimize novel drugs that can attack blood cancer stem cells. These drugs interfere with a target protein, and will prevent relapse of disease.
Impact (as written by the applicant)	By targeting blood cancer stem cells, these compounds can be used to treat and prevent recurrence of cancer in patients. In the future, we will extend this use to other types of cancer.
Major Proposed Activities (as written by the applicant)	• Test several thousand chemical compounds, which are similar to drugs, for their ability to directly stop the protein from carrying out its function • Test a small number of compounds, some of which we have already identified, to see if they interfere with blood cancer stem cells • Analyze the chemistry behind the compounds that work against blood cancer stem cells, and use this knowledge to optimize and build better versions of the compounds for future clinical trials
Statement of Benefit to California (as written by the applicant)	It remains difficult for physicians to treat some forms of acute leukemia, where relapse occurs due to the persistence of leukemic stem cells. The completion of this project will lay the groundwork for future clinical development of drugs targeting these cells via a novel post-transcriptional pathway, which will benefit several thousands of Californians, including many who are from historically underserved populations, who are diagnosed with acute leukemia each year.
Funds Requested	$1,384,347
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 85

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

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

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• As the target, IGF2BP3, is overexpressed in leukemias with MLL translocations, an efficacious drug coming out of this small molecule screen could provide a new avenue of treatment. • This grant comprises a small molecule drug screen directed against the target IGF2BP3, an RNA-binding protein that is over expressed in leukemia cancer stem cells (LSCs). • The proposal is to extend a pharmacological approach to inhibit LSCs into a screen and, subsequently, validate candidate compounds.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• The applicant will conduct a screen to identify small molecules that inhibit IFG2BP3, based on preliminary studies showing that over expression of this protein leads to hyper proliferation of hematopoietic stem and progenitor cells (HSPCs), while having no effect on overall hematopoiesis. Cells that over express IFG2BP3 seem to have higher rates of leukemogenesis, suggesting the over expressed IFGBP3 acts as an oncogene. • There is some concern that some of the critical target validation studies (e.g., knockout of IGF2BP3) has been done only in mice. In the knock out mice, LSCs seem to be increased, but there is some concern that this has not been fully validated in a human system. • The applicant proposes a small molecule screen to identify compounds that inhibit the association of RNA with IFG2BP3. The proposal contains suggestive data that support the notion that IFG2BP3 is an LSC-specific cancer stem cell marker.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 14	• Well-written grant. • Yes. This grant may yield new pharmaceuticals that can potentially treat certain leukemias, and reach a stage where translational trials on these compounds could be considered. • This is a resubmission of a grant previously reviewed by CIRM. The applicants state in their response to the previous review that they have increased their standards in the compound screen and now have a hit rate 3-fold or so lower. This may increase the ability to process what is still a large number of compounds that need to be further evaluated.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 14	• Yes. This team has already made a lot of progress in this screen and in validation testing of potential compounds.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 14	• The applicant notes that leukemias are prevalent in the LatinX population in higher proportion.
No: 0	*none*

Application #	DISC2-13441
Title (as written by the applicant)	A new precision medicine based iPSC-derived model to study personalized intestinal fibrosis treatments in pediatric patients with Crohn's disease
Research Objective (as written by the applicant)	We propose to discover a tool that will utilize patient specific iPSC-derived human mini-guts to identify personalized antifibrotic treatments in pediatric Crohn's disease patients
Impact (as written by the applicant)	The major bottleneck in intestinal fibrosis research is the difficulty in obtaining patient-specific biologically relevant cells for in vitro modeling. This iPSC-derived tool would overcome it.
Major Proposed Activities (as written by the applicant)	• Procurement of patient specific cells from pediatric Crohn's disease patients that have intestinal fibrosis (months 0-3) • Reprogram each patients harvested cells to form induced pluripotent stem cells (months 3-9) • Determine compounds via high throughput screening that attenuate the fibrotic response in each patient's iPSC-derived cells (months 9-15) • Validation of candidate compounds in corresponding biopsy-derived cells (months 15-18) • Transcriptome comparison between paired iPSC-derived cells and biopsy derived cells (months 18-24)
Statement of Benefit to California (as written by the applicant)	Crohn's disease is a recurring inflammatory disorder that affects the intestine. The number of patients that suffer from Crohn's disease in the US continues to rise each year. There are numerous patients who have Crohn's disease in California and 20-30% of these patients will require surgery due to intestinal fibrosis. There is no therapy to prevent or treat intestinal fibrosis, but the tool proposed would establish a platform that would allow numerous therapies to be tested in a personalized manner
Funds Requested	$776,340
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 85

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

Mean	84
Median	85
Standard Deviation	3
Highest	88
Lowest	75
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	10
(1-84): Not recommended for funding	5

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 15	• Overall, yes. The applicant proposes to bank iPSC-derived myofibroblast cell lines from Crohn's disease patients in a biorepository. They will provide these cells to researchers conducting high-throughput screens of antifibrotic therapeutics. I am concerned, however, that interpretation of the data remains too complex for many research teams, which will limit the near-term utility of the tool. • Yes. If iPSC derived organoids can stand in for complex whole organs, represent the pathology of Crohn's disease, and produce myofibroblasts, this will be a critically important tool. • Yes. A potential cell bank of Crohn disease patient cells is attractive and could be used by researchers to develop and screen therapeutics.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• As a proof of concept and tool validation proposal, the rationale is sound. However, it's not clear that iPSC-derived myofibroblasts will function well as high-throughout drug screening tools. I don't see sufficient preliminary demonstration of shared pathobiology between iPSC-derived myofibroblasts and primary myofibroblasts from the gut. • The utility of the proposed fibrosis model remains unclear. The applicant may be able to induce a fibrotic phenotype in their iPSC derived organoids, but their evidence for this so far is limited to upregulation of fibrosis genes. This evidence is correlative rather than a true a demonstration of shared biology. • I feel the applicant's approach of driving iPSC derived cells to a fibrotic phenotype with a cytokine (TGF-beta) has potential limitations. Crohn's is a complicated disease with a lot of variability; a model that relies on a single causal pathway may be a stretch. Still, the bank would have some value. • The major strength of the application is the applicant's validation strategy for demonstrating shared pathobiology between iPSC derived myofibroblasts and biopsy myofibroblasts. This group has a published protocol for deriving myofibroblasts from their iPSC based organoids.
No: 1	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 13	• The drug screening aspect of the proposal is less developed, but the strategy to develop and validate patient derived myofibroblasts is appropriate.
No: 2	• The need to better address fibrosis in Crohn's disease patients is an urgent need. This application is about developing a model that may enable future testing of compounds. Designing a proposal focused on validation, first, would improve clarity. • The plan lacks details for how compounds will be screened and criteria to be used to identify promising drug candidates. These would be future Milestones. • As discussed, primary patient myofibroblasts and iPSC-derived myofibroblasts may not respond similarly in screening assays. In this case, the utility of providing iPSC-derived cell lines for distribution is significantly diminished. The applicant indicates that if this occurs they will proceed with "further refinement" of the system. This does not provide insight into how this significant pitfall would be addressed. • While producing iPSC-derived mesenchymal cells from Crohn's disease patients for screening is an appropriate first step, I do have concerns about the extensive analyses that end users of the cell lines will need to undertake.
GWG Votes	**Is the proposal feasible?**
Yes: 14	• Yes. The applicant has track record of generating iPSC derived mesenchymal cells. • I think the application would be strengthened by inclusion of a collaborator with interest and infrastructure to perform drug screens using these lines.

	• Maybe. It would be helpful to know how patients will be selected. • The validation of iPSC derived myofibroblasts with those from biopsies is the key, and provides an internal control and validation that is critical considering the heterogeneity in the disease and presentation across patients.
No: 1	• I believe the ability to create the iPSC bank is in place. The high throughput screen and planned analysis of the results require additional planning.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 15	• Racial and ethnic diversity are accounted for to some degree. Gender is not discussed. • The tool does have the potential to serve the unmet medical need across the diverse population of California. • Crohn's disease impacts all populations including underserved communities. Donors will include patients from underrepresented populations.
No: 0	*none*

Application #	DISC2-13512
Title (as written by the applicant)	Modified RNA-Based Gene Therapy for Cardiac Regeneration Through Cardiomyocyte Proliferation
Research Objective (as written by the applicant)	Efficacious and safe intramyocardial delivery of modified mRNA encoding cell cycle regulators as a gene therapy for cardiac regeneration through resident cardiomyocyte proliferation.
Impact (as written by the applicant)	This project would provide disease-modifying gene therapy for people with heart failure due to loss of cardiac muscle, a leading cause of deaths in the US, using novel modified mRNA delivery.
Major Proposed Activities (as written by the applicant)	• Human iPS-derived cardiomyocytes successfully transduced with modified RNA (modRNA) encoding human cell cycle regulators • Successful delivery of modRNA encoding cell cycle regulators into mouse hearts • Successful stimulation of human cardiomyocyte division in a dish and adult mouse cardiomyocytes in vivo with modRNA delivery of cell cycle regulators • Efficacy of modRNA delivery of cell cycle regulators on improving ejection fraction in mice with acute myocardial infarction (MI) • Efficacy of modRNA delivery of cell cycle regulators on improving cardiac function in chronic post-MI rats • Evaluate safety parameters for modRNA delivery of cell cycle regulators in mice and rats
Statement of Benefit to California (as written by the applicant)	Heart disease is a leading cause of mortality and end-stage heart failure carries a 50% two-year mortality. Few treatments are available and even those do not alter the basis for disease, resulting in ultimate need for heart transplant. We propose gene delivery mediated by modified mRNA, as used in COVID vaccines, to reprogram adult cardiomyocytes transiently into a proliferative state for cardiac regeneration, thereby improving heart function.
Funds Requested	$1,565,784
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 85

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

Mean	84
Median	85
Standard Deviation	2
Highest	87
Lowest	80
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	10
(1-84): Not recommended for funding	5

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• Current treatment approaches to improve cardiac function after myocardial infarction are limited. Cell therapy approaches using various stem cell derived cell types have shown only limited success. The proposed approach to induce cardiomyocyte cell proliferation represent an innovative and promising novel approach. • Inducing cardiomyocyte proliferation to restore cardiac function following myocardial infarction (MI) could impact the unmet medical need of improving quality of life of heart disease patients. • If successful the project would require a single or small number of doses as opposed to the lifelong care needed for patients experiencing heart failure. • The proposed project represents a step toward translation. This team identified the genes that were delivered via adenovirus. Here they move toward a different delivery method and investigation of safety and efficacy in a mouse model. This is a logical approach toward translation given the early stage of the technology.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• The concept of utilizing and potentially inducing the proliferative capacity of cardiomyocytes is sound and well supported by preliminary data. • Strong preliminary data demonstrate a proof-of-concept of the approach in stimulating cardiomyocyte proliferation in multiple model systems and improving cardiac function in vivo. • Preliminary data illustrate delivery of modRNA to cardiomyocytes via intracardiac injection. • Reactivating the cell cycle in quiescent cardiomyocytes is a promising approach to stimulate cardiomyocyte proliferation and cardiac remuscularization. • Transient modRNA expression of cell cycle activators is likely to be safer than viral approaches. • The lack of targeting and expression specificity is a concern that will be investigated in this project. • Given the lack of control it may be difficult to tune the patient response to achieve the needed amount of cardiomyocyte (and other cardiac cell type) proliferation.
No: 2	• The modRNA expression timeframe is very short. ModRNA expression only happens within 24 hours. • Expression window is too short to achieve mature cardiomyocyte proliferation but multiple doses that are not targeted have a high risk to induce cardio fibroblast malignancy.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 10	• The milestones are well developed and presented. The experiments for all milestones are well described and proposed measurements are well established. • Consideration of both acute and chronic MI models is a strength. • Complementary use of human and rat cardiomyocytes in vitro, and mouse in vivo models are a strong way to address the spectrum of effects of delivery. • Innovative mouse models enable tracking cardiomyocytes that have proliferated. • The revision has expanded the safety analysis to longer time frames. • The previous critique raised the concern of potential side effects. This will be addressed in this revised application. The proposed experiments to analyze and estimate toxicity and carcinogenicity are appropriate for the current stage of the project. • Consideration of tumorigenesis is strong, but other off-target effects are not investigated as deeply. Preliminary data show substantial liver uptake, for example. Effects on liver

	proliferation may be important to study in more detail as a result. Also, cardiac remuscularization involves more than myocyte proliferation. Effects on vascularization, fibrosis, immune response, etc. are only briefly discussed. • It isn't clear how targets of cell proliferation are established or how dosing can achieve these goals.
No: 4	• Timelines are not long enough. • Proposed therapy could have off target effects.
GWG Votes	**Is the proposal feasible?**
Yes: 12	• Given the preliminary data, the outcome and goals are appropriate. • Clear quantitative milestones are provided. These are reasonable in both time and significance. • The team is highly qualified. • The team is a pioneer in cardiac regeneration and reprogramming and has the expertise to complete the proposed project.
No: 2	• This project has a fatal flaw. After injection of modRNA into hearts, all the cells receiving modRNA will express the gene. It is possible cardiac fibroblasts will transform into cancer cells after expressing these four genes. They did not provide sufficient alternative approaches. For example, what if cardiomyocytes do not proliferate after modRNA delivery? What if cardiac fibroblasts transform into cancer cells after modRNA delivery?
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 14	• Race, ethnicity, sex and gender diversity are appropriately addressed. • Black males and females disproportionately experience heart disease. A therapy that can restore heart function would serve unmet needs in this community and more broadly in diverse communities in California. • The team proposes consideration of sex and the use of diversity outbred mouse lines as future work. The proposal would be stronger if the diversity considerations were integrated at this stage of translation.
No: 0	*none*

Application #	DISC2-13510
Title (as written by the applicant)	An hematopoietic stem cell (HSC)-based approach to treat HIV employing CAR T cells and anti-HIV broadly neutralizing antibodies.
Research Objective (as written by the applicant)	We propose to transduce hematopoietic stem cells (HSCs) with vectors that encode HIV-targeted CARs (for expression in differentiated T cells) *and* anti-HIV broadly neutralizing antibodies (for expression in differentiated B and/or plasma cells).
Impact (as written by the applicant)	Recent immunotherapy approaches are limited by the rise of escape mutants. Our approach addresses this issue through the expression multiple CARs and multiple secreted bnAbs in one HSC-based therapy.
Major Proposed Activities (as written by the applicant)	• Vector construction and evaluation. • Studies of disease modifying activity; i.e., whether our immunotherapy better controls HIV-associated viremia and effectively reduces the proviral reservoir.
Statement of Benefit to California (as written by the applicant)	HIV is a devastating viral disease that affects over 140,000 Californians and well over one million Americans. Though antiretroviral therapies have significantly reduced the severity and transmissibility of the disease, a cure still remains elusive. Additionally, anti-HIV drugs need to be administered for life and have been associated with significant toxicity. The studies proposed here are intended to develop a cure for HIV.
Funds Requested	$1,143,600
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 84

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

Mean	84
Median	84
Standard Deviation	2
Highest	90
Lowest	80
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	7*
(1-84): Not recommended for funding	7

* See Minority Report below

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 13	• Achieving a sustained HIV remission or cure is of the highest priority in the HIV field. This intervention has the potential to deliver that. • Yes; the proposed product could be curative for HIV patients. • In the proposed product, an engineered hematopoietic stem cell (HSC) provides a cellular therapy that would keep HIV in check. While antiretroviral therapy (ART) is effective, a drug free approach would have many advantages. This candidate addresses the unmet medical need for a curative treatment for HIV. • Yes. However, it's worth noting that in the near term, the cost of an autologous cell therapy would be limiting as compared to ART. • Anti-HIV CAR T therapies have had modest effectiveness to date. The concept of a dual therapy consisting of HSCs engineered to generate CAR T cells as well as bnAB-secreting B cells is a promising approach. While this is a risky project, the potential payoff in improving patient care justifies the risk. • The proposed project comprises preclinical proof-of-concept in relevant in vitro and in vivo models. It represents an important bridge between discovery and translation.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• Yes. Both bNabs and CAR T cells have been shown to be effective. This project combines both of them, thereby maximizing the immune intervention. • The strength of using HSCs rather than peripheral blood mononuclear cells (PBMCs) is that the HSCs, which are earlier-stage progenitors, will home to bone marrow and provide a sustained and renewable source of effectors in vivo. However, as for all novel HIV therapies, we can't predict efficacy within the HIV reservoir. • The premise of a dual therapy consisting of HSCs engineered to generate anti-ENV CAR T cells and bnAb-secreting B cells is promising. The potential synergy within this strategy is worth investigating. • Engineering HSCs (instead of PBMCs) in this way provides potential long-term surveillance and prevention of emergence of HIV from latent reservoirs. • Preliminary data convincingly establish the promise of the candidate therapy in vitro and in vivo. • Overall, yes, though the two vector approach might may a poorer safety profile as compared to single vector therapies.
No: 1	• The addition of a CAR construct to HSCs will likely interfere with these early-stage progenitors' ability to undergo proper selection in the thymus. As a result the approach is very high risk until we see preliminary data showing these therapeutic HSCs differentiating properly into all T cell types, in vivo, while carrying this CAR.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 11	• The proposal is beautifully written with clear rationale for the proposed experiments, potential pitfalls and alternative approaches well outlined, and some very thoughtful additional experiments proposed. • One minor quibble: The applicant states that the reservoir is stable, but multiple lines of evidence now indicate that the replication competent reservoir declines (slowly) when a patient is taking anti-retroviral therapy. Furthermore, more advanced assays for evaluating the reservoir have emerged, e.g., intact proviral DNA assays, although they require large volumes of cells and therefore may not be feasible in the humanized mouse. • Overall, yes. However, T cell functionality is not sufficiently addressed. • Overall yes. However, it's possible that the two vector approach won't be a safe option.
No: 2	• The constitutive expression of the CAR could interfere with T cell development and function. This element should be de-risked with preliminary data on transduced HSCs before this proposal is funded. • The project is logically designed to test a proof-of-concept of the dual CAR T and bnAb therapy in a preclinical mouse model but overall, I have some concerns: ◦ The milestones are logically organized to evaluate various dual therapy vectors using both lentiviral and transposon delivery.

	• Experiment design is logical and detailed. Clear optimization approaches are provided prior to moving to in vivo evaluation with a subset of the candidates. Appropriate characterization assays and controls are provided. • The major weakness is that CAR expression has been shown to negatively impact T cell development. Constitutive CAR expression in other cell types is a concern as well. • The preventative milestones are interesting from a scientific point of view but unlikely to be relevant in terms of translation. This is of minor concern since the reduction in viral load are very relevant. • Assessment in various model systems appears fairly comprehensive. Consideration of in vitro release criteria is a strength. • Success criteria for each milestone are generally appropriate but would benefit from more precise, quantitative benchmarks.
GWG Votes	**Is the proposal feasible?**
Yes: 11	• The proposal is clearly feasible. It isn't clear that the approach will be effective, but it is very important to do these experiments. • Success criteria for each milestone are generally appropriate but would benefit from more precise, quantitative benchmarks. • The applicant may need to consider a method to express the CAR only in T cells as well as a strategy to prevent expression in Tregs (and other suppressive cells), since HSCs will also differentiate into suppressive immune cells.
No: 2	• Expression data are not provided for all of the proposed transgenes. The applicant should either provide expression data for every transgene, or reduce the number of proposed transgenes in the project. • The proposal does not provide demonstration of the functionality of modified NK cells.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	• Yes. HIV has disproportionate effects within racial and ethnic minority communities. Better strategies to prevent and control HIV would serve unmet needs in these communities. • HIV disproportionately affects underserved communities in California including Blacks, Hispanics, and gender minorities. This project will provide a potential therapeutic strategy that would benefit all people with HIV. • The project will use available HSCs which will presumably include diverse donors, which is positive. However, the current project plan does not provide for conclusive investigation of the potential influence of patient diversity on therapeutic outcomes.
No: 0	*none*

MINORITY REPORT

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

Seven GWG panelists scored the application 85 to 90 (funding recommended); seven GWG panelists scored the application 80 to 83 (funding not recommended). Overall, most GWG panelists voted 'yes' on whether the applicant had met each of the five review criteria: success of the project would address an unmet need, the rationale for the approach is sound, the project is well-planned, the project plan is feasible, and the proposal addresses the needs of underserved groups.

The panelists who scored 85 to 90 (funding recommended) were optimistic about the dual transgene approach using both CAR T and neutralizing antibodies, noting that CAR T therapies developed to date for HIV had shown some effectiveness. These high-scoring panelists had similar thoughts about the risks of failure as the lower-scoring panelists (see below), but this was combined with enthusiasm for the potential payoff for patients. One high-scoring panelist wrote, "The project is a preclinical proof-of-concept in relevant in vitro and in vivo models. It represents an important first stage bridging discovery and translation."

The panelists who scored 80 to 83 (funding not recommended) noted concerns that the therapeutic HSCs would not properly differentiate into all types of mature T cell in vivo, therefore limiting the safety and/or efficacy of the therapy.

Application #	DISC2-13475
Title (as written by the applicant)	Developing gene therapy for dominant optic atrophy using human pluripotent stem cell-derived retinal organoid disease models
Research Objective (as written by the applicant)	We will develop a gene therapy for a major inherited optic nerve disease and test its effectiveness by analyzing healthy and patient stem cell-derived mini human retinas.
Impact (as written by the applicant)	The research will use stem cell-based methods to overcome the shortage of human retinal cells for testing of novel therapeutic treatments for blinding diseases.
Major Proposed Activities (as written by the applicant)	• Using stem cell technology to derive mini human retinas and to identify impaired cellular functions of patient retinal neurons by comparison to healthy human retinal neurons • Using stem cell-derived mini retinas to determine the capacity of patient retinal neurons to survive under normal and stressed growth conditions • Using stem cell-derived mini retinas to examine the abnormal levels and forms of the mutant protein produced in patient's retinal cells, thus identifying the key deficiency of the disease • Using stem cell-derived mini retinas to study the physiological properties of patient's retinal neurons and determine the visual functional deficits • Producing the gene therapy vehicles for delivering the functional proteins to patient's retinal neurons • Using stem cell-based mini retinas to test the gene therapy vehicles for their capacity to transduce retinal neurons and to recuse the disease pathology
Statement of Benefit to California (as written by the applicant)	This proposed research will yield the first therapeutic candidate for treating dominant optic atrophy. Since the defective mutant gene can also cause Parkinson's disease, the study may facilitate a broader research in neurodegenerative diseases, thus benefiting Californians. The research will strengthen the leading position of California in stem cell technology by circumventing the shortage of human retinal cells and accelerating drug discovery for major blinding diseases including glaucoma.
Funds Requested	$1,345,691
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 84

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

Mean	83
Median	84
Standard Deviation	2
Highest	85
Lowest	79
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	7*
(1-84): Not recommended for funding	8

* See Minority Report below

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• Yes. The proposed work could result in a gene therapy for dominant optic atrophy (DOA), a disorder of the output neurons of the retina that deliver visual signals to the brain (retinal ganglion cells, RGCs). • This proposed product is a gene therapy for dominant optic atrophy (DOA), an optic nerve disorder caused by mutations in the gene OPA1. Treatment of DOA would address an unmet need. • Yes. However, it is unclear if the therapy can be delivered in vivo and restore RGC function. This project's impact depends on the value of the retinal organoid model the applicant has used. • This proposal uses a stem cell disease-in-a-dish model of DOA. Thus, it touches on two CIRM interests--gene therapy and stem cell research.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 9	• Yes - it is clear that OPA1 mutations are a key cause of DOA. The overall rationale is that an organic model of DOA (with resident OPA1 mutations) can be used as a platform to develop gene therapy approaches. • Yes. The applicant has validated the rationale by showing that retinal organoids with the relevant OPA1 mutations express RGC-specific markers.
No: 5	• No. I don't feel there is sufficient justification for using retinal organoid modelling instead of further developing animal models. • No. It's unclear whether the applicant's gene therapy, which uses an overexpression approach, will work in OPA, which is a dominant negative condition. • Augmentative gene therapies like this one are mainly used for recessive autosomal conditions. However, gene augmentation might work for OPA, based on preliminary data. • Not yet. If possible, the applicant needs to show that OPA1 (as a dominant Mendelian disease) has exclusively a loss-of-function mechanism, and therefore would respond to gene replacement. Alternatively, the applicant must make a strong argument that gene augmentation is a meritorious therapeutic path for this type of disease.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 13	• Yes. The applicant provides an admirable amount of preliminary data. • The applicant puts forward a solid plan for an AAV approach. • The applicants have made improvements to their plans for AAV vector design in Milestone 5. Serotype is now considered, as well as the promoter choice for driving OPA1. • I think the applicant's responses to prior critiques are on point.
No: 1	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 13	• Yes, though feasibility is predicated on the mechanism(s) of action underlying disease-causing OPA1 mutations. • Yes - the Project Plan is feasible in a 2-year study period.
No: 1	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**

Yes: 14	• The Proposal recognizes that racial/ethnic minorities bear a proportionate share of the DOA burden of disease. • Yes. As part of their Project Plan, the investigators will generate OPA1 mutant iPSC lines from DOA patients with a range of OPA1 mutations, from a range of races/ethnicities, and from both sexes. • No concerns.
No: 0	*none*

MINORITY REPORT

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

Seven panelists gave the application a score of 85 (recommended for funding); eight panelists scored from 79 to 84 (not recommended for funding). Nearly all Grants Working Group (GWG) panelists agreed that the application met four of the five review criteria: success of the project would address an unmet need, the project is well-planned, the project plan is feasible, and the proposal addresses the needs of underserved groups. However, the Grants Working Group was divided (9 voting 'yes,' 5 'no') on whether the applicant met criterion two - the provision of a sound rationale for the therapeutic approach.

The eight GWG panelists who scored the application 79 to 84 (funding not recommended) were uniformly concerned about using a gene replacement (or "augmentation") therapy for a dominant Mendelian disease. In a dominant Mendelian disease, such as dominant optic atrophy (DOA), a person carrying a single mutant copy (of two copies in the person's genome) will have the disease. The mechanism of dominance varies from disease to disease; it can be either haploinsufficiency (where one healthy copy is insufficient for health) or dominant negative function (where the mutated copy is actively harmful). The mechanism of Mendelian dominance underlying DOA is not known.

The seven panelists who gave the application a score of 85 (funding recommended) agreed that the rationale for gene replacement will be weaker if DOA has a dominant negative mechanism. However, these panelists were optimistic based on the "admirable amount of preliminary data" from patient-derived retinal organoids transduced with the candidate therapy, in which the cell type that degenerates in DOA appeared to show recovery.

Application #	DISC2-13413
Title (as written by the applicant)	In Utero Treatment of Duchenne Muscular Dystrophy with Non-viral Gene Editing
Research Objective (as written by the applicant)	To develop a lipid nanoparticle/mRNA complex that can safely and efficiently edit muscle stem cells in utero, correct the dystrophin mutation, and develop a treatment for Duchenne muscular dystrophy
Impact (as written by the applicant)	If successful, we will have developed an effective and low-cost treatment for Duchenne muscular dystrophy and a robust method to safely and efficiently edit muscle stem cells in utero
Major Proposed Activities (as written by the applicant)	• Develop lipid nanoparticle (LNP) formulations containing either M6P-cholesterol or folate-PEG-DSPE (month 1 – month 6) • Develop LNP formulations that can efficiently deliver mRNA to MuSCs and muscle fibers in Ai9 mice via in utero injection (month 4 – month 7) • Correction of the point mutation in the D2-mdx mouse MuSCs by LNP/mRNA complexes in vitro (month 2 – month 12) • Correct the mutation in D2-mdx mice after in utero injection of base editor mRNA/LNP complexes (month 6 – month 18) • Evaluate the editing efficiency and DMD phenotypic correction in D2-mdx mice after in utero base editing (month 6 – month 24) • Correct the point mutation in human DMD patient cells with ABE(NRCH)-LNPs (month 15 – month 20)
Statement of Benefit to California (as written by the applicant)	Duchenne muscular dystrophy is a long-term degenerative disorder that involves extortionate medical expenses, amounting to an annual average cost of over $50,000 per patient. Since our proposed treatment consists of a low-cost, single injection, we predict significant improvements in health care costs and medical treatment plans with the potential to be accessible to low-income patients and patients in underdeveloped and underserved medical communities.
Funds Requested	$1,221,980
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 84

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

Mean	81
Median	84
Standard Deviation	5
Highest	85
Lowest	70
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	6*
(1-84): Not recommended for funding	8

* See Minority Report below

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 11	• The proposed work will test the use of gene editing in utero to correct mutations using lipid nanoparticle (LNP)/mRNA complexes and develop LNP formulations that will target muscle stem and progenitor cells. • There is clear unmet clinical need to develop life-saving treatments for MDS-Duchenne patients. • There is an unmet need here. Duchenne Muscular Dystrophy (DMD) causes significant remodeling of the structure of muscle, as well as considerable loss. This has been a major concern with other potential DMD therapies, because there is a question of how much muscle remains to be corrected, as well as if some additional treatment will be required to restore full functionality. • The PI provides preliminary evidence in support of the notion that in utero delivery of LNPs can effectively transduce relevant cell targets, using a reporter mouse model system. • If these new LNP/mRNA candidates are shown to be successful as per the proposed work, then there is a high degree of likelihood that these findings will lead to new therapies to improve patients' lives. • The use of in utero intervention via gene editing has the potential to achieve correction in a larger proportion of cells than postnatal intervention. • Current therapies for this condition have significant limitations. • Lower cost and smaller dosage as compared to other possible treatments makes this a more accessible option. • Point mutations make up a smaller proportion of causative mutations, as compared to deletions for example. There should be some consideration of the wider patient population and the limitations of this approach. • It is far from clear that the strategy will be successful or applicable to the variety of DMD mutations in the patient population.
No: 2	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• The rationale to use lipid nanoparticles for targeted gene editing in utero is sound. The murine model selected is also appropriate, given the similarities between its phenotype and the clinical presentation of DMD. • The main rationale for the work is solidly based on previous work by the PI and preliminary evidence in support of the main approach, which is to target muscle stem/progenitor cells within a fetal context by in utero delivery of LNP/mRNA constructs. • The preliminary data are compelling and also highlight the importance to target the fetal period, as LNP/mRNA delivery to adult mice did not result in the same gene reporter efficiency or allowed muscle tissues to be targeted. • Preliminary data shows that delivery of mRNA is feasible but is some way off from demonstrating a significant degree of gene correction. • Although the applicants wish to target muscle stem cells it is unclear how this will be achieved other than by chance.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 12	• The prosed work is outlined as three main Aims. The first aim is focused on developing improved LNP formulations to better target muscle stem/progenitor cells. This aim also proposes to test these LNP/mRNA formulations in vitro and in vivo, with a reporter mouse model, similarly to the approach shown in the preliminary results.

	• Aim 2 will address the function of the new LNP/mRNA formulations using a dystrophin mutant mouse model, and test for the efficiency of gene correction and muscle function • Aim 3 will test the function of the new LNP/mRNA in vitro using patient-derived cells. • The plan seems fairly well designed. However, Aim 3 depends entirely on the success of Aim 2, with no considered alternative if it proves to be unsuccessful. • The provided preliminary data could be bolstered by better demonstrating the ability to correct at the needed level of expression.
No: 1	• Careful assessment of efficacy and safety. • The base editing construct might enhance specificity and reduce off-target effects. • Not clear efficiency of targeting will be sufficient to achieve required 15% gene correction. • Intrahepatic injection in mice may not be a good model for human in terms of pharmacokinetics.
GWG Votes	**Is the proposal feasible?**
Yes: 11	• The applicants have much needed prior expertise, considerable resources, and a strong supportive collaborative network, and have structured their plan around these advantages. This increases the feasibility of the proposed project. • Yes, the proposed aims are well structured and feasible within the outlined timeframe. • Investigators have experience in appropriate technologies. • Too many milestones. Human studies in 6 and 7 seem outside scope of application; focus should be on studies in vivo.
No: 2	• Too ambitious. • The feasibility is unclear.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 12	• The applicants appear to have carefully considered the importance of diversity and inclusion, supplemented by various institutional resources. • The PI points out and addresses these factors in the proposal.
No: 1	• Consideration is given to these points. The financial impact of this disorder is high.

MINORITY REPORT

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

Six panelists gave this application a score of 85; eight panelists scored between 70 and 84. The great majority of panelists voted 'yes' as to whether each of the five review criteria were met.
Overall, reviewers in favor of funding the application thought there was a significant unmet need for Duchenne Muscular Dystrophy (DMD) treatments and thought that the approach of using lipid nanoparticles for targeted gene editing in utero made sense. These reviewers also thought the preliminary data were strong, the proposed project was highly innovative, and the team was well-qualified to complete the work. One supportive reviewer noted that the dependency of Aim 3 on the success of Aim 2 was a potential risk for the project as no alternatives were presented.

The greatest divergence between high scoring (funding recommended) and lower scoring (not recommended) panelists is in the comments for criterion 4: feasibility of the project. Reviewers in favor of funding thought the timeline was feasible and the team was qualified; reviewers not in favor of funding said the project was too ambitious, uncertain, and/or had too many milestones. No reviewer expressed doubts about the proposed team.

Application #	DISC2-13442
Title (as written by the applicant)	Microgel encapsulated iPSC-derived notochordal cells to treat intervertebral disc degeneration and low back pain
Research Objective (as written by the applicant)	We aim to discover an injectable, rejuvenating treatment for painful intervertebral disc degeneration using microtissue-encapsulated iPSC-derived notochordal cells (iNCs) using large animal models
Impact (as written by the applicant)	Our treatment candidate may allow for a non-invasive stem cell therapy, targeting the underlying pathogenesis of intervertebral disc degeneration, the leading cause of chronic back pain in adults.
Major Proposed Activities (as written by the applicant)	• Optimization, characterization and deliverability testing of iNC-loaded microgels, microtissues or bulk hydrogel as therapeutic candidates for injectable treatment of intervertebral disc degeneration. • To demonstrate the safety and efficacy of iNC-loaded microgel/microtissue and iNCs injected in bulk hydrogel in inhibiting disc degeneration in a large animal model.
Statement of Benefit to California (as written by the applicant)	Intervertebral disc (IVD) degeneration associated low back pain is a leading cause of disability. While it affects all adults, it is prevalent in underserved communities that more often carry government-sponsored health insurance. Despite decades of research, there are no robust therapies targeting the underlying causes of IVD degeneration. Spinal disc injections with the proposed treatment candidate may provide an IVD rejuvenating, inexhaustible, off-the-shelf treatment accessible to all.
Funds Requested	$1,342,606
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 83

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

Mean	83
Median	83
Standard Deviation	3
Highest	86
Lowest	80
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	6*
(1-84): Not recommended for funding	8

* See Minority Report below

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• The proposal addresses a regenerative therapy to treat chronic lower back pain resulting from intervertebral disc regeneration. The use of induced pluripotent stem cell (iPSC)-derived notochordal cells is a promising treatment to meet this significant medical burden. • The candidate is an iPSC-derived cell therapy in a fibrin microgel. It has the potential to improve quality of life in patients with degenerated discs and chronic lower back pain. • The project proposes development of this therapy in a large animal model, which is appropriate for translation. • The premise for regeneration is not yet established. The likelihood for success could be increased by further analysis in vitro or in small animal model. • This is a new grant that is premised on the team's prior CIRM funded study that demonstrated the intradiscal injection of iPSC-derived notochordal cells delivered in bulk-hydrogel can survive in the degenerated intervertebral disc and have the potential to rejuvenate lower back discs. • Intervertebral disc degeneration is believed to be the major source of chronic back pain, and more than 90% of surgical spine procedures are performed because of consequences of this degenerative process. • Current clinical treatments for discogenic pain focus on the alleviation of symptoms rather than targeting the mechanism of underlying disease. • Literature studies suggest the use of cell-encapsulating microgels can alleviate the damage to cells caused by host environment. Embedding of iPSC-derived notochordal cells into microgel and pre-conditioning culture in vitro to form microtissue prior to injection is expected to allow for matrix deposition of the cells prior to injection and protect the cells from the unhealthy environment, leading to an accelerated and potentiated healing process. • Successful completion of this project will lead to the identification of a novel injectable therapeutic candidate for back pain and intervertebral disc degeneration. The results should demonstrate efficacy of the therapeutic candidate, the safety of its use in immunocompetent animals, and mechanism of action of the cell-microgel/microtissue in a large animal model. • Development of an allogenic stem cell therapy will allow for an off-the-shelf treatment accessible to different population groups suffering from painful intervertebral disc degeneration. However, the proposed therapy could also become autologous and patient specific.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• The premise of using an iPSC-derived notochord cell product for treating intervertebral disc degeneration is sound. • Notochord cells have repair capacity in the intervertebral disc but are few in number in adults. During development, notochordal cells give rise to mature nucleus pulposus disc cells. In humans, the notochordal cell population vanishes at the age of 10. • Since humans develop age-dependent intervertebral disc degeneration, it has been suggested that notochordal cells are essential for maintaining a healthy intervertebral disc and would be the ideal cell type to regenerate lower back discs. • The team provides preliminary data illustrating their process of differentiating iPSCs to notochord-like cells, and their ability to deliver these cells into a large animal model. • The applicant's publication describes a novel method of deriving notochord cells from human iPSCs. As a test article, the iPSC-derived notochord cells showed no sign of teratoma formation in Nog/SCID mice. In a Yucatan large animal model, the test article (delivered in GelTrex) prevented intervertebral disc degeneration using iPSC-derived notochordal cells over 8 weeks. • In preliminary animal studies, the applicant used MRI-based non-invasive measurement of tissue pH in the disc to demonstrate a correlate of efficacy in vivo. • Embedding of iPSC-derived notochordal cells into microgel and pre-conditioning culture in vitro to form microtissue prior to injection is expected to allow for matrix deposition of the cells prior to injection. This matrix may enhance healing and offer protection against the

	inflammatory environment. Preliminary data, in vitro or in vivo, would demonstrate feasibility. • Preliminary proof-of-concept studies used Geltrex, a synthetic basement membrane hydrogel, for delivery of notochordal cells to the nucleus pulposus (center of the intervertebral disc). This material is derived from murine tumor cells and would not be clinically translatable. • Injection of iPSC-derived notochordal cells in GelTrex led to survival of the cells in the degenerated intervertebral disc, retention of the notochordal cell phenotype, a protective effect in terms of pH levels, and morphological changes characteristic to intervertebral disc degeneration. However, these studies did not show complete regeneration or new matrix formation. • The lack of regenerative capacity of the Geltrex test article in preliminary studies seems to raise the level of risk in this approach. • Preliminary data showing iPSC-notochordal cell matrix production in this hydrogel would strengthen the proposal. • In their publication, the team stated that in the future studies they planned to optimize biomaterials; this proposal aims to do so. • The motivation for including microgel, microtissue, and bulk hydrogel in the planned studies should be made clear in the proposal. • Fibrin gel is a thermo-responsive, fibrinogen-derived, commercially available hydrogel in wide clinical use. The microgel used the proposed product is also thermo-responsive and fibrinogen derived. However, it has tunable biomechanical properties and supports cell attachment better than fibrin gel. • There appear to be significant preliminary data.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 9	• The team will test the hypothesis that micro-encapsulated iPSC-derived notochord cells can attenuate intervertebral disc degeneration and reduce low back pain. iPSC-derived notochord cells. Microgels are fabricated beads developed using a microfluidics platform. These microtissues are pre-conditioned (21 days, hypoxia, and NP media) cell product-microgels. • The project plan includes complementary in vitro and in vivo studies to optimize cell delivery.
No: 5	• The choice of fibrinogen as a hydrogel is not justified. Chemical and mechanical properties of a gel have significant effects on cell behavior. • Qualitative attributes of the cells after differentiation are not discussed. • Consideration of stability of the cells is a strength. However, the results presented only show viability, not potency. • The path from transcriptomics and immunofluorescence analysis in Aim 2 to mechanism of action is underdeveloped. • The applicant needs to better characterize the cells to be used for treatment.
GWG Votes	**Is the proposal feasible?**
Yes: 14	• Viability milestones are quantitative. Potency milestones would benefit from quantitative metrics. • The team is well-equipped to perform the proposed study. They have expertise in this type of cell differentiation and in studies using the models and experimental techniques. • All aspects of the proposal appear to be doable. Some additional preliminary data demonstrating the iPSC functionality to produce extracellular matrix would be important. • I'm not confident about the markers proposed for nucleus pulposus phenotyping – are these markers from the current state of the art?
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 14	• Race/ethnicity- and sex-based bias is described for the management of the target disease.

	• The project will use female large animals since females have a higher predisposition to disc damage. However, significant numbers of males also suffer from disc degeneration. • All communities suffer from chronic back pain, with underserved communities having higher incidence. A regenerative therapy would benefit all of California. • Disc degeneration and lower back pain affect the general population.
No: 0	*none*

MINORITY REPORT

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

Six panelists gave this application a score of 85 to 86 (funding recommended); eight panelists scored 80 to 83 (not recommended). All fourteen scoring Grants Working Group (GWG) panelists agreed (with a 'yes' vote) that the application meets four of the five review criteria: success of the project would address an unmet need, the rationale for the approach is sound, the project plan is feasible, and the proposal addresses the needs of underserved groups. Panelist votes were split (9 'yes', 5 'no') on whether the application meets review criterion 3 for a well-planned and well-designed project.

Panelists who scored the application 80 to 83 (funding not recommended) emphasize the importance of additional preliminary data demonstrating the cell product's functionality in its final formulation.

Panelists scoring 85 to 86 (funding recommended) were favorably impressed with the study rationale and the applicant's published study results showing derivation of notochordal cells from iPSCs. These panelists also made positive comments about the strength of the preliminary data generally and the feasibility of the project. High-scoring panelists acknowledged the need for supportive data from studies using the final candidate product but thought that the project plan put the applicant in good stead to collect this data during the project period.

Application #	DISC2-13502
Title (as written by the applicant)	Excitatory spinal interneurons from human pluripotent stem cells to treat spinal cord injury
Research Objective (as written by the applicant)	The primary objective of this research is to test whether excitatory human V2a spinal interneurons engineered from human pluripotent stem cells (hPSCs) can repair the damaged spinal cord and restore motor function.
Impact (as written by the applicant)	Currently there are no existing therapies to repair the injured spinal cord. Our therapeutic cell candidate - hPSC-derived human V2a spinal interneurons - could address this significant unmet medical need.
Major Proposed Activities (as written by the applicant)	• Activity 1: Develop a Good Manufacturing Practice (GMP)-compliant PSC line that yields optimal V2a donor populations. • Activity 2: Define the optimal dose of transplanted Good Manufacturing Practice (GMP)-V2a neurons that can be safely administered to the injured spinal cord. • Activity 3: Assess the time it takes for donor cells to anatomically integrate into the damaged spinal cord and repair motor networks. • Activity 4: Determine the minimal amount of time necessary for transplanted V2a neurons to functionally connect to injured motor networks and contribute to recovery. • Activity 5: Determine the therapeutic efficacy of transplanted V2a neurons derived from GMP-compliant hPSCs to form functional motor circuits following spinal cord injury.
Statement of Benefit to California (as written by the applicant)	Spinal cord injury (SCI) is a permanently debilitating condition resulting from traumatic injury that renders individuals partially or fully paralyzed. The associated life-time health care costs are exorbitant (millions of dollars) and the ongoing need for assisted care impacts family members and friends. A reparative cell therapy for SCI that could restore motor function would benefit the autonomy of the individual and enable a fuller return to society, thereby improving quality of life.
Funds Requested	$1,560,728
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 83

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

Mean	83
Median	83
Standard Deviation	3
Highest	86
Lowest	77
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	5
(1-84): Not recommended for funding	10

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• The goal of this proposal is to repair motor circuits that are damaged in cervical spinal cord injury. This is an important unmet medical need. • The proposed technology comprises human pluripotent stem cell (hPSC)-derived excitatory spinal V2a interneurons (V2a SpINs) for transplantation into the injured cervical spinal cord to restore function to injured respiratory and forelimb networks. The transplantation of selective excitatory interneurons that can successfully serve as a relay to form synapses with motor neurons above and below the level of the injury could provide improved neurocircuitry repair and motor function after SCI. • Cervical level SCI is the most common of SCI, and have most severe health and quality of life consequences. Even modest improvement in function could have high impact. • Cell transplantation for spinal cord repair has been and will continue to be an avenue of interest for SCI, but faces a number of hurdles including complexity in rebuilding damaged neurocircuitry in a meaningful way. • The proposed human PSC-derived candidate, V2a SpINs, provides a well-defined relevant population of excitatory interneurons to integrate as a relay over damaged spinal regions for restoration of some descending motor pathways. • The expected candidate is planned to address technical barriers in the ability to utilize stem cell-based therapies for restoration of spinal neurocircuitry following SCI by optimizing purification of a selected therapeutic cell phenotype, generating expandable, bankable, and readily available human PSC cell source, and utilizing GMP-compliant cell lines. • The vision for progression includes translational steps to scale up production of V2aSpINs and establish GMP-compliant banks. Rigorous safety testing (tumorigenicity, immunogenicity) is also planned, as well as other steps towards preparation of a Pre-IND meeting with FDA. • The use of allogeneic donor sources is rational based on the ability to fully characterize the batch cell source and maintain available pools as needed for acute SCI treatment. However, the necessity for immunosuppression, perhaps over a long period, may be detrimental as well as face compliance issues, and should be addressed moving forward to translation. • The proposed work is at fairly early preclinical stages, with a number of additional intervening steps needed for upscaling towards translation. • The research is still early stage but there potential for high impact.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• The proposal is based on strong prior publications showing both functional improvement in rodent SCI models by rat V2a NPCs and the ability to generate selective populations of the desired excitatory spinal V2a neurons from human PSCs that can be developed for clinical use. • More precisely defined sources and phenotypes for targeted therapeutic transplantation is now becoming feasible with advances in hPSC technologies and differentiation protocols. • The envisioned therapeutic product is a bankable population of GMP-compliant defined V2a spinal interneurons that can be readily available for treating SCI. • Strong supportive preliminary data showing good hPSC-V2a differentiation, phenotypic maturation time course, and reproducibility, with no glial cell populations under the current differentiation protocol is included. • Introduction of the optogenetic control of V2a activity resulted in convincing responsivity to light stimulation on in vitro arrays.

	• Preliminary data using the human V2a transplants in post cervical SCI shows cell survival and evidence of neurite extension. • Preliminary data using channel rhodopsin-expressing donor cells suggests increased phrenic motor activity with stimulation, indicative of functional connectivity in this system. • The project is fully focused on enabling technologies for advancement of stem cell-based therapies in the treatment of SCI. • Previous publications and preliminary data provide solid rationale for the proposed studies. • There are some prior indications of transplantation of neurons into the injured spinal cord may enable establishment of a functional circuitry, and the general concept is sound.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**

Yes:
12
	• The project is planned to meet the program objectives by readying a translatable process for selective differentiation of the desired human V2a excitatory spinal interneuron phenotype, derived and banked for GMP compliance and readiness, for use in CNS repair.
	• A number of in depth progressive steps to accomplish the goals of the project with well-defined milestones are included in the plans.
	• The overall plans and milestones are clear and comprehensive, and should lead to maximizing the optimization potential of the selected V2a phenotype (differentiation, cell dosing, repair timing) as well as a thorough and complementary set of outcome measures (behavioral, physiological, anatomical) for in depth understanding of transplant fate and function.
	• Synaptic integration using transsynaptic tracing and functional integration using optogenetic stimulation of reporter and activatable V2a-SpINs should provide needed mechanistic support for continuing development of this approach if promising outcomes are obtained.
	• Focus on the phrenic motor system and diaphragm function is a strength and an area of expertise of the team.
	• In response to the previous critique, some clarifications regarding the focus on the respiratory motor network as primarily a “test bed” have been added, and explanation that the technology is envisioned as potential repair for other motor systems.
	• Although transplanted V2a SpINs can extend axons over 5 mm in rats, it is unclear whether this would be sufficient for creating the anticipated neural relays in larger areas of injury in human SCIs.
	• The evaluations of maximal feasible cell dose for efficient and safe transplantation are important but it is unclear how this information will be used for upscaling to the human spinal cord and lesion cavities.
	• The revised program now utilizes immunosuppressed rats (daily cyclosporine A) instead of nude rats, in response to previous critique, and has included some preliminary data suggesting this is feasible. Nevertheless, work in other labs has suggested that cyclosporine A may not be sufficient for long-term xenograft survival (human to rat) and could be a confound in these studies in longer term follow-up.
	• Overambitious, but most of the proposed studies are logical.
	  ◦ Ten iPSC lines will be tested but these are not identified (two companies are listed but nothing more).
	  ◦ Selection criteria for iPSC lines is based on their capacity to generate CHX10+ V2a Interneurons (>70%). However data shown in Fig. 3 (n=8 hiPSC lines) show significant variability and none more than 70%.
	  ◦ The applicant does not discuss the need of having a cGMP compliant manufacture protocol and the scalability of the procedure.
	• They have a good ability to generate the desired spinal interneurons from human PSCs, although it's not clear they can achieve the desired level of semi-purity.
	• The project has attractive features of using optogenetically engineered cells combined with electrophysiological recordings of recovered muscle activity, anatomical and behavioral analysis and viral tracing to verify synaptic connectivity.
	• Excellent preliminary data.

No:	*none*

2	
GWG Votes	**Is the proposal feasible?**
Yes: 10	• Preliminary studies are promising. Transplantation of cells one week after cervical contusion injury demonstrates survival of the transplanted cells, which extend neurites both rostral and caudal to the injury epicenter, with cells being detected at one and three months after transplantation. Immunohistochemistry suggested generation of synapses, and retrograde labeling from the diaphragm revealed donor cells integrated with a phrenic network. • The weakness is that there are no functional data related to recovery in spinal cord injury with the proposed neurons. That said, previous studies from this group on interneurons differentiated from mouse embryonic stem cells transplanted into a cervical contusion injury showed recovery of respiratory function. Thus, there is prior data indicating that recovery of function is a possibility with this approach. • A concern is that Milestones 1-4 are anticipated to all be completed by the end of year 1 with a smooth progression in order to proceed with Milestone 5, which will take at least a full year 2. This may be problematic should any technical issues or unexpected outcomes arise. • The Principal Investigator (PI) has over a decade of experience in developing cellular therapeutics to treat spinal cord injury, including cervical injuries, respiratory deficits, and rodent NSC V2a transplants. The PI's former mentor is a consultant on the project. A Co-Investigator will help guide the single cell aspects of the study. A respiratory therapist has been added to the team in response to previous reviews. • The Principal Investigator (PI) has a strong background and training and the support of the institute director. There is some concern with the PI's limited experience in overseeing a major team project. The PI is currently in a Postdoctoral position, with promotion to Staff Scientist contingent on receiving this proposed award. • Supportive Core facilities are available at the institute. • The resources for all of the human PSC differentiation studies and analyses are in place. • Although the rat facility is described, there is no mention of availability of plethysmography chambers, motor testing (Montoya staircase and Digi-gait), or any pain testing set-up. • The budget is appropriate for the research proposal.
No: 4	• The applicant has recruited several partners in response to concerns expressed in a prior review of this application. However, while the Principal Investigator (PI) has a promising career trajectory, he or she was not a co-author on the publications that led to the project, and he or she does not have adequate experience to lead a project of this magnitude.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 14	• There is a discussion that underserved communities are disproportionately affected by consequences of injury at both acute and chronic stages, furthering the socioeconomic burden. The developed therapy is envisioned to be readily applicable to all individuals regardless of race, ethnicity, sex or gender, and ultimately become more affordable with rapid advances in cellular therapeutics technologies. • Both male and female rats will be used in the planned studies. • Appropriate. No concerns.
No: 0	*none*

Application #	DISC2-13438
Title (as written by the applicant)	HIV therapeutics composed of lipid nanoparticle (LNP)-mRNA complexes that edit the CCR5 gene
Research Objective (as written by the applicant)	We will develop an in vivo, lipid nanoparticle (LNP)-delivered gene editing system to transfect patients' hematopoietic stem and progenitor cells (HSPCs), edit the CCR5 gene, and cure HIV-AIDS.
Impact (as written by the applicant)	We will develop a therapeutic for HIV-AIDS based upon acid degradable lipid nanoparticles that contain a gene editing system comprising Cas9 mRNA and gRNA. We will also develop a methodology for transfecting hematopoietic stem and progenitor cells (HSPCs) in vivo.
Major Proposed Activities (as written by the applicant)	• Edit the CCR5 gene in HSPCs with acid degradable LNPs that deliver Cas9 mRNA and gRNA • Protect macrophages from HIV infection via editing of CCR5 in HSPCs with acid degradable LNPs • Develop a formulation that can deliver GFP mRNA to 50% of HSPCs after a direct bone marrow injection or an intravenous injection • Develop a formulation that can deliver Cas9 mRNA and gRNA to HSPCs after a direct bone marrow injection or an intravenous injection and edit > 50% of the CCR5 gene in HSPCs • Prevent HIV infection in humanized-mice via a direct injection of acid degradable LNPs into the bone marrow • Develop a formulation that can prevent HIV infection in humanized-mice after an intravenous injection
Statement of Benefit to California (as written by the applicant)	Acid degradable LNPs will have significant advantages over current gene editing therapies for HIV. For example, a therapeutic based upon acid degradable LNPs that directly edits HSPCs in vivo after intravenous or intraosseal injection will be orders of magnitude cheaper than a bone marrow or autologous stem cell transplant and significantly easier to adhere to than life-long ART, resulting in improved patient outcomes and lower community spread in California.
Funds Requested	$1,015,476
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 82

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

Mean	83
Median	82
Standard Deviation	4
Highest	90
Lowest	80
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	4
(1-84): Not recommended for funding	11

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• Achieving virological remission of HIV infection is of the highest importance to the field. • The proposed technology is acid degradable lipid nanoparticles (LNPs) for Cas9 mediated disruption of CCR5 in hematopoietic stem and progenitor cells (HSPCs). This project addresses the unmet medical need of a curative approach to HIV. • CCR5 is a co-receptor for HIV entry into CD4 T-cells. Previously, bone marrow transplants of CCR5-nonfunctional HSPCs into HIV+ individuals have shown functional cure. • Numerous strategies have been explored to block HIV-CCR5 interactions and results have been promising (e.g. ZFN targeting of CCR5). • This proposal focuses on LNP optimization, targeting to HSPCs, and demonstration of CCR5 editing in vitro and in vivo in a humanized mouse model. This translational project would generate a candidate ready for later stage translational evaluation (e.g. large animal model). • LNP-associated editing of cells in vivo, including hepatocytes, suggest that the approach is viable. • LNPs delivering CRISPR/Cas9 for elimination of CCR5 in HSPCs may provide a feasible method to edit CCR5 in vivo using delivery systems that have been proven safe during the COVID19 pandemic.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 10	• A small number of HIV+ patients have already been cured of HIV infection through stem cell or cord blood cell transplantation from individuals with nonfunctional CCR5 genes. Thus, the approach has strong rationale. • The principle of blocking CCR5 to prevent HIV is quite sound, although some strains can utilize the CXCR4 co-receptor in place of CCR5 for entry. • Individuals with X4-tropic virus would not be cured by this approach. However, strategies to knockout CXCR4 are already being developed, and could potentially be incorporated into this LNP-based technology as well. • The peripheral blood CD4+ T cell reservoir is not addressed in this proposal. PBMC CD4+ T cells could replicate HIV for years before finally decaying away. Humans are not humanized mice. • The numbers of cells that would need to be transfected to achieve the aims of the proposal are quite large. I am concerned about the potential impact on HSPC differentiation in general as well as the oncogenic potential. • Off-target effects of CCR5 modification would be a concern. • Although benefit would likely outweigh this risk, potential immune deficits introduced by disabling CCR5 should be noted. People with homozygous CCR5 mutations have increased symptomatic West Nile Virus infections as well as worse flu outcomes (see Ellwanger JH et al. Virus Research 2020; 286:198040). • Preliminary data demonstrate advances in LNP generation via acid degradability, presumably accelerating endosomal release. The team demonstrates high levels of transfection of HSPCs with these LNPs. • Preliminary data showing LNPs delivering Cas9 and a gRNA to HSCTs are convincing. • Preliminary data support efficacy in the humanized mouse model. • Targeting of CCR5 with lipid nanoparticles is a valid approach for in vivo editing that mitigates issues of accessibility and affordability. • The project is uniquely enabled by editing HSPCs.
No:	• Preliminary data are insufficient.

4	
GWG Votes	**Is the proposal well planned and designed?**
Yes: 12	• The proposal is well-designed to optimize LNP formulation and targeting for transfection of HSPCs in vitro and evaluation of CCR5 editing in a humanized mouse model. If successful the candidate will be in a good position for translation. • Yes. The optimization of the acid degradable LNPs is well described, as are the humanized mouse experiments. • A systematic plan is provided to screen and optimize LNP composition for transfection efficiency. Experiments are well-designed to leverage in vitro optimization and in vivo evaluation. The formulation studies are likely to lead to improvements in LNP delivery. • Use of HSPC-specific antibodies to target LNPs is a logical approach. Off-target effects are considered in the experimental design. • The parameter variation in the LNP formulation is difficult to follow. Parameter space and optimization strategy are vague. • Experiment design is rigorous and statistical analysis strong. Controls are clearly described. • Analysis of protection from HIV in the humanized mouse model with CCR5 edited is quite comprehensive • Humanized mice will be treated with LNPs and infected with HIV. It is not clear that the JRCSF HIV strain has tropism for macrophages and also not clear why the investigators will test for infection of macrophages instead of CD4+ T cells. • I'm not convinced the applicant needs to include studies of the impact of the transfections on macrophages. The majority of HIV replication (including for CCR5-tropic HIV) occurs in CD4+ T cells, which also produce more virus (per cell) than macrophages. • Donor variability in HSPCs is not adequately considered. • Yes. However, I see this proposal as a strong technical approach but a weak application of the technology.
No: 2	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 11	• Yes. The aim is proof-of-concept that LNPs targeting CD7 with CRISPR/Cas9 for CCR5 editing can reduce viremia in mouse models. • LNP formulation F10 can successfully deliver GFP mRNA to HSPCs. Improvements will be made to the lipids for enhanced stability and targeting. • c-Kit may not be the best target for HSPCs, but CD45 is an immune-restricted target.
No: 3	• The applicant does not provide data to support their goals for HSPC transduction efficiency. They may wish to review Cardozo-Ojeda et al. eLife 2021;10:e57646. "Thresholds for post-rebound SHIV control after CCR5 gene-edited autologous hematopoietic cell transplantation." The authors of that article concluded that transplanted HSPC need to be fivefold higher than residual endogenous HSPCs and that the fraction of protected HSPC in the transplant achieves a threshold 76-94%. • It isn't clear that the study will be able to achieve the high level of editing needed for therapeutic remission. • However, the team is outstanding. Investigators have complementary expertise in LNPs, HSCs, HIV/virology, and gene editing. The team has translation/commercialization experience and members are renowned leaders in their fields.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 14	• HIV infection disproportionately afflicts Blacks, Hispanics, and gender minorities in California. If successful, the proposed intervention would benefit all people with HIV. • HIV affects underserved racial/ethnic communities disproportionately. If LNP-based gene editing to treat HIV is effective, it would serve a major unmet need for the diverse population of California. • The research plan considers sex of the mice. • The plan does not consider influence of diversity or other sources of heterogeneity in the HSPCs . • The acid-degradable gene editing platform developed here could be adapted to other diseases that affect diverse populations.

	• LNP mRNA complexes can be formulated for millions of different people, and could be a method to serve the needs of underserved communities.
No: 0	*none*

Application #	DISC2-13514
Title (as written by the applicant)	Engineered Human Stem Cell-Derived Pancreatic Islets Encapsulated in a Thin Film Device for Patients with Type 1 Diabetes
Research Objective (as written by the applicant)	We propose engineered human stem cell-derived islets encapsulated in a thin film device to restore blood sugar levels in diabetes, without the need for insulin injections or systemic immunosuppression
Impact (as written by the applicant)	Our work would overcome the three major bottlenecks for cell replacement for diabetes: dearth of supply, poor engraftment and function of beta cells, and requirement for lifelong immunosuppression.
Major Proposed Activities (as written by the applicant)	• Identify, obtain, achieve scale-up, and perform quality control analysis for at least six human pluripotent stem cell lines that meet donor eligibility criteria and are consented for commercial use • Identify at least one donor eligible, commercially-consented human pluripotent stem cell (hPSC) line that yields engineered islets that display glucose-stimulated insulin secretion in vitro • Determine function of donor-consented, engineered islets in vivo in diabetic immunodeficient mice • Determine functionality and immune protection of encapsulated engineered islets in vivo in diabetic immune competent mice
Statement of Benefit to California (as written by the applicant)	Type I Diabetes (T1D) is a significant burden in California, especially for children; according to estimates provided by the California Diabetes Program, ~2.3 out of every 1,000 children between the ages of 5-19 in California had diagnosed diabetes in 2008, with 83% having T1D. Research proposed here would represent a significant step towards the holy grail of T1D treatment: a therapy for patients without the need for the administration of insulin, frequent blood testing, or immunosuppression.
Funds Requested	$1,458,825
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 82

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

Mean	81
Median	82
Standard Deviation	4
Highest	85
Lowest	75
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	4
(1-84): Not recommended for funding	11

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 13	• The applicant proposes a combination product comprising functional stem cell (SC)-derived beta cells within an immune isolation device for transplantation into a confined site. This approach addresses current limitations in the field of beta cell replacement for treatment of Type 1 Diabetes (T1D). • This product would significantly improve patient care. It does address several bottlenecks in the use of stem cells to treat T1D, including immunosuppression issues and lack of cadaveric pancreatic tissue for transplantation. • Engineered islet cells combined with two other cell types are encapsulated in a polymer based device and placed under the skin to produce insulin in response to increases in blood glucose. The device needs to be vascularized and then evade immune destruction in order to work. If this is successful, it would have a large impact on disease treatment and quality of life. • The applicant's engineered beta cells show superior function in preliminary studies. • The immune isolation device has been well validated and characterized by the applicant. • T1D is a disease where current treatment options are less than ideal. • This is potentially high impact but not very novel.
No: 1	• This proposal is technically sound, but not novel. Many research teams plan to use encapsulated beta cells for the treatment of Type 1 Diabetes (T1D).
GWG Votes	**Is the rationale sound?**
Yes: 12	• The applicant has compelling preliminary data; these were expanded in the resubmission. Concerns remain as to (i) whether the engineered beta cells will actually reverse diabetes after transplantation, and (ii) whether the device truly demonstrates immune protection for xenografts in the applicant's human cells into mice study. • The encapsulation device appears to block IgG diffusion which should protect cells from allo-immune rejection. This may also prove to make it more biocompatible. Indeed, preliminary data show the product can produce insulin for at least 42 days. • The combination of cells within the device appears to help mature the engineered beta cells. However, there appears to be a significant time lag from implantation to maturation. How will patients manage this transition? • Yes, but the preliminary data are not compelling. For example, as shown in Figure 3, in a mouse model of T1D, the device was not able to regulate blood glucose to normal levels. • Overall yes, the rationale is sound.
No: 2	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 8	• The project plan includes well-described milestones with clear, quantitative outcomes. • The applicant has adequately addressed dose response issues and immune evasion issues. • The applicant may not be able to produce high quality beta cells from human Pluripotent Stem Cells (hPSCs). Their beta cells secrete much less insulin as compared to published reports from other labs. • The applicants have made reasonable responses to previous reviews. • Yes. However, this product might face a high bar for regulatory approval.
No: 6	• The approach lacks sufficient novelty.
GWG Votes	**Is the proposal feasible?**
Yes: 11	• This is a very ambitious plan for the two year timeline, but it is appropriately focused on defining a product for translation. • This is a strong team with complementary expertise. • This is a well-written and easy to follow proposal with a project plan that proceeds logically. Potential setbacks have been addressed. While there are many hurdles to

	bringing this product to clinical trials, information gathered from these experiments will certainly advance the field. ● The applicant has addressed several pitfalls (scalability, future regulatory approval, optimization of the device (pore size, structure) cell number, dose response, vascularization) with workaround strategies. Unfortunately, some of these alternative strategies would make for a very complicated product from a regulatory perspective. ● Overall, yes. However, this project may require three to four years of effort. Additionally, the team would benefit from engaging an experienced stem cell biologist with expert knowledge of beta cell differentiation from hPSCs.
No: 3	● The project is too early stage to achieve the outcome of the Quest award (a final candidate for translation).
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	● The application includes a thorough explanation of how the project will address the needs of underserved communities. ● The project could prove beneficial to the full, diverse California population as many underserved communities are disproportionally affected by T1D. ● The product would help to reduce costs and longer term issues with the disease, which represent a significant burden among underserved communities. ● No concerns.
No: 1	*none*

Application #	DISC2-13396
Title (as written by the applicant)	Reprogramming Somatic Cells into iPSCs Engineered with an Anti-PSCA CAR to Develop Allogeneic Off-the-Shelf Cell Therapy to Treat Pancreatic Cancer
Research Objective (as written by the applicant)	Our candidate product (PSCA-CAR_s15 uiNK) is derived from transduction of iPSCs selected from the most ideal source and episomally reprogrammed from mature NK cells or CD34+ cells.
Impact (as written by the applicant)	Cell Functionality and Quality; Scale up and Manufacture
Major Proposed Activities (as written by the applicant)	• Development and characterization of induced pluripotent stem cells (iPSCs) via somatic cell reprogramming of various human cells • Selection of good iPSC candidate lines by testing NK cell differentiation potential of UCB-iPSCs, CD34-iPSCs, NK-iPSCs, and T-iPSCs • Engineering the selected iPSC candidate(s) with deficiency of B2M, replacement of CIITA with HLA-E, and expression of PSCA-CAR_sIL-15 • Hematopoietic differentiation towards CD34+ cells and NK cells from the CAR u-iPSC cell line • In vitro cytotoxicity of BCMA CAR-NK cells, expansion, and freezing as an "off-the-shelf" product • In vivo evaluation of iPSC-derived PSCA-CAR_s15 NK cells
Statement of Benefit to California (as written by the applicant)	Our goal is to develop an "off-the-shelf," ready-to-use cell therapy that is appropriate and easily accessible for any patient regardless of race, ethnicity, sex, gender, age, or socioeconomic status. By leveraging an effective, innovative, safe, and standardized off-the-shelf cell therapy to kill tumor cells and energize latent immune responses, we expect our results to have a positive impact by ultimately reducing mortality for patients suffering from devastating and deadly cancers.
Funds Requested	$1,358,100
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 82

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

Mean	81
Median	82
Standard Deviation	2
Highest	85
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/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 13	• The project is scientifically very interesting and has *potential* for impacting an unmet medical need (pancreatic cancer), but there are significant concerns with regard to regulatory hurdles and the feasibility of getting to trial, particularly in the academic setting. • The project uses cord-blood-derived induced pluripotent stem cells (iPSCs) differentiated into natural killer (NK) cells and then gene-edited for hypoimmunogenicity (knockout of B2M and CIITA and knock in of HLA-E), and transduced with a lentiviral vector encoding an anti-PSCA chimeric antigen receptor (CAR), soluble IL-15, and a reporter/suicide switch. • The applicant has considered many aspects of product development including good manufacturing practices (GMP), pre-clinical safety and efficacy studies, and dosing studies. • However, regulatory approval will be a big challenge. This is not addressed in a satisfactory way. Specifically, the applicant cites interactions with FDA regarding cord-blood derived non-gene-modified NK cells. This is completely different from, and practically irrelevant to, iPSC-derived, gene-edited, AND transduced NK cells. There is very little precedent for the proposed product, and none in the academic setting. • Universal NK modified cells hold potential as commercializable products for refractory disease like pancreatic cancer. The experience of the investigative team is expected to catalyze and accelerate stem cell discoveries. • The proposal targets a large unmet need. • The iPSC-derive nature of the product can support off-the-shelf use.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 9	• The science is sound. The proposal is innovative. It includes well thought-out controls for chimeric antigen receptor (CAR) function and models for testing antigen expression. • However, there are no studies describing measurements of off-target effects, genome integrity, homogeneity of the product, or even comparison to cord-blood derived NK cells. The rationale for doing this with iPSC-derived NK cells instead of cord-blood derived NK cells is not clear. • The preliminary studies using cord-blood derived NK and also iPSC-derived cells are convincing. • The rationale is sound and the reporter/suicide switch is attractive.
No: 4	• The applicant needs to address possible adverse effects of gene editing.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 7	• I have doubts that the proposed product could readily advance to translation but perhaps an INTERACT meeting could put this in order. Overall, it is a well-constructed, quality project. • Some potential pitfalls are identified, but not all. Regulatory hurdles are not adequately considered. Also, how will the investigators determine purity and identity with this kind of product? Will there be purity at the genome level? • The project plan and timeline are suitable. • Integrity of the genome is not discussed - this will be a hurdle in FDA discussions. • Pitfalls are considered to some extent, but the section could use more depth.
No: 7	• No; there are gaps in the planning. • There is a lack of attention to safety concerns with heavily gene-edited cells.

	• The biology and rationale for the number of lines, and for testing the lines at each of the engineered steps, is not provided. • Pitfalls are well-integrated, but less so for potential pitfalls associated with dosing, pharmacokinetics, and pharmacodynamics.
GWG Votes	**Is the proposal feasible?**
Yes: 11	• As proposed, yes, but regulatory issues are a bit glossed over. • The institute has tremendous resources; the team is outstanding; the timeline is realistic; the budget is appropriate; the proposal is feasible. • The proposed team is excellent; the applicant has decades of experience in this area.
No: 3	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	• If successful, the therapy will be universal. • Yes, the project serves the needs of underserved communities. • This is addressed.
No: 1	*none*

Application #	DISC2-13488
Title (as written by the applicant)	Targeted Biocoated Mesoporous Silica Nanoparticle Delivery of an RNAi Therapeutic to Cancer Stem Cells in Recurrent/Refractory Ovarian Cancer Models
Research Objective (as written by the applicant)	Our objective is to use a novel nanoparticle method to deliver inhibitor to tumors. It will be targeted using a lock and key like mechanism, and will inactivate stem cells so tumors cannot recur.
Impact (as written by the applicant)	Our therapeutic targets advanced ovarian cancer, where only 30% of women survive 5 years. Over 70% will have a recurrence, and less than 30% of women with recurrent disease respond to chemotherapy.
Major Proposed Activities (as written by the applicant)	• Develop a surgical recurrent model of ovarian cancer where human cancers grow in the mouse ovary, then are surgically removed, and time to recurrence is observed. • Test the impact of targeting the Snail/let-7 axis on stem-ness and recurrence of ovarian cancer by employing biocoated mesoporous silica nanoparticles to protect and deliver RNAi targeting cancer stem cells. • Design and initiate studies on measures of identity, activity, and purity, mechanism of action, pharmacokinetics, and early safety, to complete a draft target product profile. • Enhance the diversity and scope of patient-derived samples, to expand the ethnically diverse biobank, and characterize the molecular subtype of samples. • Elucidate the functional effects of manipulating the Snail/let-7 axis in ovarian cancer subtypes in vitro: determine best biocoating and knock down strategy. • Determine mechanism of action by defining regulatory networks transcriptionally activated by the Snail/let-7 axis; identify altered pathways and validate gene expression changes.
Statement of Benefit to California (as written by the applicant)	In California, there will be 2,250 ovarian cancer diagnoses, and 1,390 deaths, in 2022 (American Cancer Society projection). Over 70% of diagnosed ovarian cancers will recur and those that do, rarely respond to treatment. Our studies will use a novel nanoparticle method to protect and deliver therapy precisely to cancer stem cells, aimed at preventing recurrence and restoring sensitivity to chemotherapy. We will advance a new therapeutic toward clinical trials for treatment of women with this deadly disease.
Funds Requested	$847,103
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 80

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

Mean	81
Median	80
Standard Deviation	1
Highest	83
Lowest	80
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• The proposed technology will develop nanoparticle-mediated RNA delivery to sensitive ovarian cancer stem cells to chemotherapy. High grade serious ovarian cancer has a high mortality rate and new, effective strategies to treat it would impact a clear unmet medical need. • Reducing stemness has the potential to increase sensitivity of ovarian cancer to chemotherapeutics. This combination therapy could significantly improve patient care. • Identification of targeted, personalized strategies could improve patient outcomes in a subset of ovarian cancer patients. • This proposal focused on a subset of ovarian cancer which is already outside the top 10 most common cancer types by incidence and by annual deaths. The technology, however, has the opportunity to be leveraged in other tumor types.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 10	• The goal of this application is to develop more effective means of delivering RNAi to tumor cells. This is based on using coated particles made out of mesoporous silica nanoparticles that are coated with materials that allow targeting to tumor cells, with a particular interest in targeting cancer stem cells. • Targeted therapeutics have been developed for many cancer types but not yet extended to ovarian cancer treatment. There is a good rationale to attempt this. • Targeting snail expression to try and increase levels of let-7 seems a reasonable approach to try, and could allow RNAi targeting of Snail. • The premise of decreasing stem-ness as a means of sensitizing cancer cells is sound. • The team provides a significant amount of preliminary data gained in a prior CIRM project that established nanoparticle RNA delivery in vitro and in PDX models. • This is a continuation of previously funded work in this space and seems like a natural progression. • Preliminary results demonstrate that Snail knockdown and let-7 overexpression reduce measures of stem-ness. • Preliminary data also demonstrate a proof-of-concept of a decrease in tumor burden by Snail knockdown. • The effects of sensitization of ovarian cancer cells is fairly modest upon let-7 overexpression. • The assumed equivalence between epithelial-mesenchymal transition and stem-ness is overly simplistic, and it's not clear that even successful reversal of epithelial-mesenchymal transition will reverse stem-ness. • Experiments demonstrating that treatment in vivo eliminates cells able to initiate tumors on transplantation (with multiple cell numbers examined) are missing, which is critical in demonstrating a targeting of cancer stem cells in vitro. • RNA therapeutics have been difficult to translate to clinical therapies because of challenges in delivery and stability, as acknowledged by the team.
No: 4	• How specific is the biocoating-based targeting in vivo? • Is Snail the best target for stem cells?
GWG Votes	**Is the proposal well planned and designed?**
Yes: 9	• The proposal outlines a reasonable and stepwise approach to reach the intended objective. • Largely yes. One of the goals is to establish a surgical de-bulking model, which would be clinically relevant. The applicants have developed clinically relevant models of patient-derived tumors.

	• They have shown that snail knockdown suppresses the cancer stem cell phenotype and increases sensitivity to repair inhibition. What about sensitivity to other agents used in treating these cancers?
No: 5	• The study is well-designed to focus on targeting Snail and let-7 in PDX models in Aim 1, and in identifying cancer subtypes susceptible to the candidate in Aim 2. • Experiments are clearly designed to meet target objectives. Experimental groups and analyses are clearly defined with important controls identified. • Experimental analysis in terms of tumor progression and characterization is fairly comprehensive. • The project takes cancer heterogeneity into account - this is a key strength. • Successful delivery and regulation of Snail/let-7 is key to success. The proposal indicates a dosing regimen but it isn't clear that this has been optimized and validated. There are not plans to investigate this more fully, other than to assess various nanoparticle coatings. • Consideration of nanoparticle biodistribution is a strength, but potential off-target effects on tissues where the particles collect should be investigated. • The use of different coatings for targeting is potentially powerful. It isn't clear that the coating strategies developed in vitro will be effective in the in vivo environment. • Mechanism of action studies are underdeveloped. While transcriptomics can be powerful, bulk RNAseq might mask effects of the treatment on small cancer stem cell populations. In addition, putative mechanisms need to be tested in more systematic studies. These MOA studies may not be directly relevant to therapeutic development.
GWG Votes	**Is the proposal feasible?**
Yes: 12	• Milestones are logically organized toward the translational goals. • The team is well-equipped to perform the proposed study. They have expertise in cancer stem cells, ovarian cancer, nanoparticle-mediated delivery and various molecular and cellular assays. • This is an ambitious project, but the PI appears to be familiar with the methods, topic, and cell lines involved. • Not clear. Despite the positives, the proposed biocoating binds to many different things, so the question of whether this can truly prove effective for targeted delivery is unclear. • Many of the success criteria would benefit from more quantitative benchmarks.
No: 2	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 14	• Ovarian cancer is limited to females. The project will use samples for a diversity of races and ethnicities. • Ovarian cancer affects a broad cross-section of the population. New therapeutics would benefit all racial and ethnic communities in California. • Cancer does not discriminate between different communities.
No: 0	*none*

Application #	DISC2-13532
Title (as written by the applicant)	Development of next-generation human cerebellar organoids to model hereditary cerebellar ataxias
Research Objective (as written by the applicant)	Next-generation cerebellar organoids will allow robust recapitulation of human cerebellar development and degeneration leading to the identification of effective treatments for cerebellar ataxias.
Impact (as written by the applicant)	Next-generation cerebellar organoids will address a bottleneck in the field by providing reliable and consistent recapitulation of human cerebellar dysfunction and degeneration.
Major Proposed Activities (as written by the applicant)	• Long-term culture of human cerebellar organoids that reproduce the cell diversity of the human cerebellum • Test the efficacy of xenotransplantation of human induced pluripotent stem cell (iPSC)-derived microglia into cerebellar organoids in improving neuronal maturation and functionality • Testing of reliable and consistent recapitulation of cerebellar neuronal dysfunction and degeneration in human cerebellar organoids derived from SCA36 patient iPSCs
Statement of Benefit to California (as written by the applicant)	In addition to improving the understanding and screening of drugs for hereditary cerebellar ataxias, our model will be a valuable resource for the broader biomedical community interested in modeling dysfunctions in other types of human brain disorders with cerebellar involvement including complex mental disorders and cerebellar cancers, by delivering the first high-throughput platform for effective drug screening in distinct types of human cerebellar cells.
Funds Requested	$834,000
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 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	2
Highest	83
Lowest	75
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 12	• Hereditary cerebellar ataxias are devastating diseases that require long-term care. Animals models have largely not recapitulated the human pathology. The proposed product could address an important bottleneck. • The applicant proposes to develop an organoid model of the human cerebellum to study cerebellar ataxia and use to screen for therapies. Cerebellar ataxia is a rare but serious disease with no current effective therapy. • Maybe. The impact of this proposal remains unclear - the application does not include any preliminary proof-of-concept studies showing the benefits of screening therapies using organoids as opposed to other culture systems. Relatedly, the proposal includes very little about how future organoid screening assays might be constructed. • The proposed product would provide a research tool for other developmental questions.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 10	• The applicant proposes to study patient-derived cerebellar organoids. They provide compelling preliminary evidence that their approach reproducibly generates cerebellar organoids containing relevant cell populations. • The process of organoid maturation includes a step wherein the applicant will transplant human iPSC-derived microglia into the maturing cerebellar organoids. This is an interesting approach, intended to promote neuronal development in the organoids in the way that microglia support neuronal development in vivo. However, cerebellar microglia are a unique cell type within the larger population of microglia that the applicant can expect to generate from iPSCs. It's not clear that iPSC-derived microglia would be suitable for promoting a mature cerebellar fate among neurons within the organoids. • Overall, yes. However the proposal's rationale does not describe a read out with clear utility for future screens. In addition, the organoids might not faithfully represent human pathobiology.
No: 2	• The applicant's approach to reducing organoid variability includes eliminating forebrain cells from the culture at an early stage. However, there are many steps after forebrain differentiation that could contribute to heterogeneity in cerebellar organoids. In preliminary studies, the applicant's cerebral organoids are appropriately patterned but quite variable. • This application would be strengthened by a comparison between the applicant's data and results from recently published protocols for generating cerebellar organoids. I would like to know what is really novel and superior about this approach.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 6	• Overall, yes. However, the applicant does need better endpoints for their studies (in addition to cell death).
No: 6	• I believe this project will produce a disease model but not a useful therapeutics screening tool. • The proposed methods for reducing variability in organoids are not clear, except for elimination of the forebrain component and generation of two progenitor populations. • The methodology has limited novelty or innovation. • The application does not include adequate consideration of the potential for development of hypoxia and cell stress in the organoids. • The applicant needs to provide or develop a quantitative means for assessing the structure of organoids. The structure of the cerebellum is complex and integral to function. • Overall the project is well-defined, but falls short of providing evidence that the pathobiology of cerebellar ataxia can be mimicked in organoid models. • While animal models have some limitations, it would be useful to incorporate insights from transgenic mouse models into the expected outcome(s) for organoid studies.

	• The potential impact of microglia transplantation into the organoids is not well described. It remains unclear whether this complex approach will be necessary or sufficient to mimic the function of the cerebellum or the pathobiology of cerebellar ataxia.
GWG Votes	**Is the proposal feasible?**
Yes: 8	• The preliminary data suggest this is feasible. • The project is feasible but not very ambitious. • The project is highly feasible and the applicants have shown that they have the relevant expertise to conduct these experiments.
No: 4	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 11	• Yes, as the applicant plans to collect iPSCs for their studies from a cohort with diverse genetic backgrounds. • Organoid models can, by definition, have utility across any diverse population.
No: 1	*none*

Application #	DISC2-13439
Title (as written by the applicant)	Establish master iPSC for targeted large-cargo integration and its application in developing safe and efficacious iPSC-CAR-iNK allogeneic product
Research Objective (as written by the applicant)	The goal is to establish master iPSC for targeted large-cargo integration and its application in developing safe and efficacious iPSC-CAR-iNK allogeneic product
Impact (as written by the applicant)	This study will overcome current bottlenecks in targeted large-cargo insertion technologies including CRISPR/Cas, base editing and prime editing in cell product development.
Major Proposed Activities (as written by the applicant)	• Generate TARGATT master iPSC line for targeted large-cargo integration • Engineer TARGATT master iPSC to express CD19CAR and iL15 • Differentiate iPSC-CD19CAR to NK cells • In vitro/in vivo efficacy and safety of CD19CAR-iNK cells targeting lymphoma
Statement of Benefit to California (as written by the applicant)	The direct benefit will be the therapeutic product CAR-iNK for the treatment of individuals with lymphoma, with lessened burden on healthcare system by providing allogeneic, efficacious, cost-effective health care solutions and increased productivity. Using iPSC-based genome editing is in line with the CIRM mission and Proposition 14. If successful, it will help California to maintain its leading role in accelerating stem cell treatments for patients with unmet medical needs.
Funds Requested	$1,128,350
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 80

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

Mean	77
Median	80
Standard Deviation	4
Highest	83
Lowest	70
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 12	• This project focuses on an alternative to the popular CRISPR/Cas9 gene editing approach, TARGATT, to develop a cell line that can be used for allogeneic stem cell transplantation and brings together several emerging technologies. • The technology described in this proposal could have an impact on developing non viral CAR-iNK product providing product consistency from batch to batch and product to product as CARs will be expressed from the same genomic locus. • The proposed project utilizes unique cargo loading into iPSC lines that could be valuable to other groups and approaches using PSCs to generate cell types. • It is unclear whether the project will have impact. Other groups and strategies have been used for CD19CAR NK generation. The product is defined, but population of patients is unclear.
No: 2	*none*
GWG Votes	**Is the rationale sound?**
Yes: 10	• Given that phase 1 clinical trial of CD19CAR-T for B-cell malignancy manufactured by piggyBac transposon reported global changes in transcription in some patients and recent lentivirally engineered CAR-T trials were put on hold due to safety concerns, the technology developed in this proposal could have an impact on the future of cell based therapies. • The team has a history with TARGATT. The preliminary data on iPSC platform methodology could be strengthened. • Rationale of why the cells are superior is not clear.
No: 4	• Novel use of TARGATT site that seems to be superior to other methods and may have less safety risks. This is a unique aspect of this proposal, including the generation of a iPSC line to serve as a general tool for cell therapies. • The novelty seems to lie in the cell line, and molecular site and cargo methods vs. the generation of CD19CAR iNKs. Use of primary cells in xenografts vs. cell lines (Raji/NALM-6/K562) should considered. • Unclear where the cell line generation work is being done, but differentiation protocols are in place. • The proposal for these targets is uninspired. • Few pitfalls in safety and effectiveness are discussed or measures of residual cells and how this will be dealt with. For example, secondary transplants or reversion of differentiation from NK cell type.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 6	• The PI aims to establish a TARGATT iPSC platform that can be used as “master cells” for safe and efficacious cell therapy product development; and also develop a CD19CAR-iNK product targeting lymphoma. • There are no details on the use of mouse models that will authentically replicate the clinical settings. The PI mentions the use of humanized NSG but no details have been provided.
No: 8	• Well designed and straight forward. • Applicants have previous experience with the technology, along with certifications to make clinical grade products for cell therapy. • Brief mention of non NK cell contamination, but no information provided about efficiency and suicide gene effectiveness, or function of NK cells from engineered iPSCs.
GWG Votes	**Is the proposal feasible?**
Yes: 11	• The proposal is feasible and well supported by collaborators. • The team is in place and budget suitable. • This is an ambitious design but the role of NK vs T CAR was unclear. • Most of the milestones seem to be logically planned except for the Milestone 4 which focuses on in vitro and in vivo testing of CD19CAR-iNK cells. This milestone should take more time than anticipated by PI.
No:	*none*

3	
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 14	• The proposed work will develop iPSC platform that can be used in patients regardless of race, ethnicity, sex, and gender. Furthermore, NK cell product has low graft-versus-host disease (GVHD) and does not require HLA type matching and therefore can include all HLA types without discrimination.
No: 0	*none*

Application #	DISC2-13409
Title (as written by the applicant)	Developing CRISPR-Cas9 genome editing as a therapy for dyskeratosis congenita (DC) and related telomere biology disorders (TBDs)
Research Objective (as written by the applicant)	The key objective of our experiments is to develop and test the feasibility of using CRISPR/Cas9 genome editing as a therapy for bone marrow failure-associated with dyskeratosis congenita
Impact (as written by the applicant)	Dyskeratosis congenita is a fatal bone marrow failure syndrome. The experiments described here will develop an CRISPR/CAS9 based intervention for patients without bone marrow donors.
Major Proposed Activities (as written by the applicant)	• Evaluating the effects of TINF2 disruptions in HSPCs with a TINF2-DC mutation • Develop safe and effective TINF2 editing reagents • Demonstrating efficacy of TINF2 editing in patient TINF2-DC cells TIN2 p.K302Lfs14* or p.R282C cells
Statement of Benefit to California (as written by the applicant)	The proposed research is designed to find a treatment for the bone marrow failure syndrome Dyskeratosis congenita.
Funds Requested	$1,083,715
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 75

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

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

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 13	• The current proposal seeks to develop a novel gene editing strategy applied ex vivo for autologous HSPC transplants to treat bone marrow failure associated with dyskeratosis

	congenita and other telomere biology disorders. Patients with these diseases have progressive telomere shortening and loss of stem cell populations with mortality resulting from bone marrow failure within the first 3 decades of life. Patients with TINF2 mutations (the target of the proposal) can have severe bone marrow failure in early childhood. • The proposed work will develop a gene targeting approach for patients with bone marrow failure syndrome dyskeratosis congenita, which arise due to exon mutations in the telomerase regulating gene TINF2. • This grant could yield a candidate treatment for Dyskeratosis Cogentia (DC), a genetic telomere maintenance disorder that manifests as bone marrow failure. • Current treatments are limited to allogeneic hematopoietic stem/progenitor cell transplants. Donor availability is even more limited in this disease because the germline nature of the mutation means matched sibling donors are not good donor candidates. Based on above, if successful, the proposed technology would address a significant unmet medical need. • The PI provides convincing preliminary evidence in support of the notion that disrupting the expression of one allele of TINF2 can rescue defects in telomere length maintenance caused by TINF2 mutations. • The main goal is to test the potential therapeutic benefit of targeting, via CRISPR/Cas9, TINF2 in patient derived CD34+ hematopoietic stem/progenitor cells (HSPCs). • The eventual therapy would involve CRISPR editing of patient-specific cells to delete a mutant TINF2 allele, followed by re-introduction of the corrected cells into the patient. This could meet an unmet need in certain telomere biology defect patients. • This is an approach that would delete a dominant mutant allele of TINF2 in patient cells, thus correcting them prior to engraftment. • The proposed experiments represent a logical approach to both establish the efficacy of the proposed technology as well as the safety (off-target). They use human HSPCs and patient derived HSPCs and thus a clear path to clinical translation is evident. They propose in vitro and in vivo studies in the mouse model. These studies will be important for clinical translation. • Yes, if these new therapeutic candidates are shown to be successful as per the proposed work, then there is a high degree of likelihood that these findings will lead to new stem cell-based therapies to improve patient care.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• The main rationale for the work is based on studies that support to the notion of targeting TINF2 in HSPCs to enable a rescue in telomerase function and ameliorate bone marrow failure in patients following autologous HSCT with TINF2 gene-targeted cells. • The rationale is based on convincing preliminary data that shows that deletion of a mutant TNIF2 by gene editing can restore telomere length in human embryonic stem cells (ESCs). • The preliminary data are compelling and also highlight the need for the proposed therapy in cases where the genetic lesion in the TINF2 is known. • An eventual therapy rests on the ability of HSPCs to restore telomere length when dominant negative TNIF2 is deleted in HSPCs. These must behave like ESCs (restoration of telomere length) in order for this approach to work, which is currently untested. If objective 1 fails, the approach for a therapeutic will fail, so this is a key piece, the success of all subsequent aims rests upon success in objective 1. • The proposed project is largely based on previous studies performed by the investigator in human pluripotent stem cells demonstrating that deletion of mutant TINF2 can restore telomere length . This supports the rationale for targeting mutant TINF2 as a therapy for DC. It is unclear if a therapeutic benefit will result from targeting the wild type TINF2 gene or is limited to targeting the TINF2 gene with the pathologic variant. • It is unclear if a therapeutic benefit will result from targeting the wild type TINF2 gene or is limited to targeting the TINF2 gene with the pathologic variant. If targeting of the pathologic variant is required, how is this specificity achieved? • Overall, the grant does not contain proof of concept preliminary data to show that HSPCs (like ESCs) have an intrinsic ability to restore telomere length. If this is

	not the case, then the proposed approach (deletion of dominant negative TNIF2 alleles) will fail. • The current project uses HSPCs. Nice preliminary data in HSPCs. Preliminary data is lacking in initial screens of the many sgRNAs proposed. Use of patient derived cells with known pathologic variants are a strength, however, the current viability of the cells and ability to use them in the proposed studies has not been demonstrated in any preliminary data.
No: 2	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 7	• The project is well constructed and designed. The milestones and plans for the project are logical and address many of the points required to move a candidate to clinical translation. • Yes, but there is some risk as telomere lengthening abilities of HSPCs have not yet been demonstrated when proper telomere maintenance genes are restored to function. • Though the grant contains pitfalls and alternatives, these mostly state that no problems are expected. • There is a lack of suggestion of alternative approaches. This is particularly true in the gene editing space in which many advancements, including potentially safer gene editing approaches, have been developed.
No: 7	• The proposed work is outlined as three main Aims. The first aim is focused on validating the targeting of TINF2, as a way to improve telomerase function in cells that will be pre-modified to carry a mutation, which leads to a dominant loss of telomerase function. This aim will test the effects of this modification in human CD34+ cells in vivo by engrafting mice, and in vitro, by testing bone marrow cells from engrafted mice. • Part of Aim 1, 1.4, has a potential weakness in the feasibility of the proposed experiment. The PI points to the high-risk & rewards and critical aspect of this sub-aim, but it does not directly consider whether it would beneficial to have a way to mark the cells bearing a mutation in one exon TINF2 after 12 weeks, to be able to give them a second hit on the TINF2 gene, this time in another exon. Given the preliminary data, the experiment does not appear to be a very feasible approach. • Aim 2 will test different molecules for effective targeting of TINF2, which would also have low off-target effects. • A key aspect of Aim 3 is the adoptive transfer of gene modified patient-derived CD34+ cells to mice to test whether this modification would in fact be sufficient to reverse the telomeric shortening. This serves an excellent test of the main hypothesis and validation of the therapeutic potential.
GWG Votes	**Is the proposal feasible?**
Yes: 12	• Yes, the proposed aims are well structured and feasible within the outlined timeframe. • Excellent team. PI is an expert in telomere biology and telomere biology disorders. A collaborator, who leads the BMT group at another institution, is an expert in the molecular principles of telomere biology disorders and is able to provide the patient derived cells to be studied in milestone 3. • The PI is an expert in telomere biology and stem cell approaches. A collaborating investigator, an expert in bone marrow failure, is also excellent. • The team has access to all the resources and expertise required for the studies. • One concern is that there is no preliminary data on the patient derived cells used in milestone 3. These cells are frozen down and a question of their viability has been noted in the proposal. The investigators note that if the cells are not viable or able to be used, then new, fresh patient derived cells will be acquired. Information on the availability/frequency of these cells would be helpful. • Yes, but the HSPCs must be able to restore telomere length when TINF2 is corrected.
No: 3	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**

Yes: 13	• The investigators note that current treatment is a matched allogenic HSPC transplant and minority communities are disproportionately affected by the lack of matched allogenic donors. Thus, the proposal addresses this point. • Yes, the PI points out and addresses these factors in the proposal.
No: 1	• This aspect is not well considered. The diversity plan seems mostly focused on recruitment of diverse research staff, rather than a focus on diverse patient populations.

Application #	DISC2-13393
Title (as written by the applicant)	Development of novel small molecules against cancer stem cells in solid cancers
Research Objective (as written by the applicant)	To study and optimize lead compounds with multi-kinase activity against existing glioblastoma stem cells and radiation-induced phenotype conversion of non-stem glioma cells into induced glioblastoma stem cells.
Impact (as written by the applicant)	Glioblastoma is a universally deadly disease. While radiotherapy prolongs survival in glioblastoma it has hit a critical barrier. The proposed study aims to improve the efficacy of radiotherapy in glioblastoma.
Major Proposed Activities (as written by the applicant)	• Define and validate the molecular targets of MXC017 and MXC079 in vitro and in vivo • Optimize the MXC017 and MXC079 to increase their activity against existing glioma stem cells and to prevent radiation-induced conversion of non-stem glioma cells into induced glioma stem cells • Perform pharmacokinetic studies in tumor-bearing mice • Demonstrate efficacy of MXC017 and/or MXC079 against glioblastoma alone and in combination with radiation in patient-derived orthotopic models of glioblastoma
Statement of Benefit to California (as written by the applicant)	Glioblastoma is a universally deadly disease and treatment outcomes have not improved in two decades. The standard-of-care for patients with glioblastoma is surgery, followed by radiotherapy and chemotherapy. The median survival is only 15-18 months. The proposed studies aim to develop novel compounds against glioblastoma that will enhance the efficacy of radiotherapy to improve survival for patients with glioblastoma, thereby improving value-based care and the life of Californians.
Funds Requested	$1,404,000
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 75

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

Mean	74
Median	75
Standard Deviation	4
Highest	80
Lowest	65
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 11	• This application focuses on generating improved treatments for glioblastoma. This is a critical medical need as the survival of patients with these tumors continues to be dismal. • Probably, but this is not entirely clear. The proposal text uses terms like "maps," "signatures," and "stemness" in unclear ways. • Glioblastoma is a major problem with a dearth of therapeutics. • Cancer stem cells represent a major problem for the elimination of tumors because they seem to be resistant to several therapeutic approaches. Drugs with the ability to differentiate cancer stem cells could greatly impact cancer treatment. • The identification of Notch pathway members as potential regulators of cancer stemness, and the identification of isoxazole derivatives as modulators of stemness, are novel contributions.
No: 3	• The project aims to improve the current standard of care for the deadly malignant brain tumor glioblastoma and improve outcomes for patients. • The project has a potential to develop novel small molecule compounds that can be used in combination with radiation therapy to inhibit the generation of glioblastoma cancer stem cells and increase the effects of radiation for patients with glioblastoma. • The project proposes to optimize key drug properties such as the blood brain barrier penetration and safety to normal tissues. They also propose efficacy studies in clinically relevant animal models to pave the way to clinical translation.
GWG Votes	**Is the rationale sound?**

Yes: 10	• A small molecule to prevent formation of glioblastoma-initiating cells during radiation makes sense.
	
	• The applicant has a strong track record of publication on research directly relevant to this proposal, and this proposal is a rational extension of the line of ongoing research.
	  ◦ The applicant has already demonstrated and published the efficacy of dopamine receptor antagonists using an analogous concept and approaches, but no data are presented that show the new compounds to be superior to dopamine receptor antagonists.
	  ◦ The applicant has identified the lead compounds and present a set of strong preliminary data showing their capacity to inhibit GBM cell plasticity post radiation, penetrate the BBB and not cause major toxicity to normal cells.
	  ◦ The proposal takes advantage of novel compounds to inhibit radiation-induced cancer stem cells to improve therapeutic effects.
	• The applicant has long-standing research program aimed at finding ways to overcome the resistance of cancer stem cells to radiation therapy.
	  ◦ In the past, the applicant developed an approved drug that prevents radiation-induced phenotype conversion of cancer stem cells and improves survival in mouse models of glioblastoma.
	  ◦ Continued screening based on phenotype conversion of cancer stem cells has produced other compounds, including two current leads (MCX017 and MCX079). Based on one of these (MXC017), the applicant has synthesized 113 novel compounds and identified chemical groups that appear to modulate radiation-induced phenotype conversion.
	  ◦ They also have identified several targets of MXC017, and these targets have biologic plausibility as pathway components in glioblastoma.
	• In preliminary studies, Isx9 treatment appears to differentiate cancer stem cells and increases the frequency of CD24+ cells through a Notch-mediated mechanism. These data suggest that treatment with Isx9 (or related compounds) may reduce the aggressiveness and chemoradiation resistance of tumors through elimination of tumor-initiating cells.
	• Details about the preliminary screen are lacking.

	• They don't provide enough detail for me to understand how their preliminary screen was conducted. In particular, what assay did they use? • The preliminary data are a bit hard to interpret. For example, Figure 2 is missing a number of labels. It appears there are other compounds that perform better than the current lead compounds. • The applicant needs to better explain the significance of Figure 2A and provide more details on the figure design (e.g., what does icon size mean?). • The grant does not read clearly to non-cancer experts.
No: 4	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 5	• They have modified their new compounds to reduce toxicity against normal murine microglial cells, murine fibroblasts, human astrocytes, and murine neural stem/progenitor cells. These are cell types with limited vulnerability. According to published findings, the most vulnerable cells to both chemotherapy and radiation are oligodendrocytes and oligodendrocyte precursor cells. Safety screens need to be done on vulnerable cells, not on cells resistant to toxic insults. • The applicant proposes to use gene expression assays to finalize their top two candidates. It's not clear this is the best approach, nor does the applicant explain what gene expression parameters will be used. • The applicant hypothesizes that their current lead compounds inhibit glioblastoma-initiating cells (GICs). They need to test this by treating cells in vitro with a clinically reasonable reagent concentration, followed by orthotopic transplantation of varying cell numbers (e.g., 10k, 50k, 150k, 500k), to confirm. • The applicant's hypothesis that the expression of reprogramming factors is related to stemness is not adequately tested. • As radiation is generally combined with temozolomide, it's important to conduct early testing with this clinically relevant combination. • The project has two Aims: 1) optimizing the two current lead compounds and 2) characterizing their efficacy and mechanism of action when combined with radiation therapy. The applicant should clarify why the current lead compounds (MCX017 and MCX079) need to be further optimized. • Use and availability of a large panel of glioblastoma PDX models enables testing in heterogenous tumor models and gives this proposal strength and clinical relevance.
No: 9	• I am not sure this is squarely about cancer stem cells. The affected tumor cells may not be stem cells. • The main variable is the identification of compounds similar to Isx9. With Isx9 in hand, the investigator provides no rationale why the experiments proposed could not be performed with this compound to develop preliminary support for their approach.
GWG Votes	**Is the proposal feasible?**
Yes: 9	• It's unclear, and unfortunately the in vivo studies required to determine the potential utility of this approach occur well into the project plan/timeline. • The major drawback to feasibility is that pre-clinical studies are a downstream consideration. Knowing whether this is a meritorious approach will come after everything else has been done. • The publication record of the applicant and preliminary data support the feasibility of this research proposal. • The applicant's planned collaborations with a medicinal chemistry expert and a neuro-oncology and PDX expert will facilitate the execution of this project. • However, the proposal is ambitious. The applicant proposed to create and test new compounds in many models, and to conduct cutting-edge multi-omics molecular analysis. This casts doubt on feasibility within the two-year time frame. • The feasibility and justification for conducting studies in twenty different models for each compound are weak. • The grant is too ambitious. Target identification, biomarker analysis, mechanism of action, and models are each tedious projects and the sum may not be completed within two years.

	• Drug screening and characterization is complex and may require more than 2 years to identify a lead compound. • The budget is appropriate.
No: 5	• The core part is feasible; the systems biology is a stretch. • Exactly what will be done? E.g., what does "comprehensive" mean? What is a map (exactly)? Are we interested in merely "illustrating" shifts, or are there some precise statistics and methods that can provide evidence for shifts? How do you quantify "more robustly"? How do you "identify subpopulations"? • The applicant must define "stemness signature" and "stemness score," and use these consistently, such we can evaluate their merits. • Why not pre-specify a particular metric for determining efficacy? • What does "network analysis" mean? It typically implies dozens if not hundreds of exploratory approaches. I am not sure an exploratory approach is appropriate for validating a lead compound. • "Principal component analysis and uniform manifold approximation and projection (UMAP) will be applied to reduce the dimensions of the data." Why do you need to reduce the dimensions? Is it possible to pick either PCA or UMAP? Why two approaches? If more than one approach is needed, why stop at two? • The choice of Benjamini-Hochberg is a good and appropriate choice for multiple test correction. • "[I]ncluding linear mixed effects and random frailty Cox models, with random effects accounting for possible patterns of partial exchangeability between mice." That seems like a lot of parameters and relatively few mice. How much power would you gain by using a simpler model with fewer parameters?
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 12	• Yes. Demographic information from the donors for the PDX models is available, and the applicant plans to use models derived from patients with diverse racial backgrounds. • Small molecules may reduce the expense of therapy and make it more accessible to economically disadvantaged patients. • Small molecules that can differentiate cancer stem cells would be highly impactful for underserved communities.
No: 2	*none*

Application #	DISC2-13450
Title (as written by the applicant)	Generation of polarization-restricted human iPSC-derived macrophages to reprogram the multiple myeloma tumor microenvironment
Research Objective (as written by the applicant)	We will develop a novel human stem cell-derived, macrophage-based cell therapy that is engineered to have enhanced anti-tumor activity to target the malignant bone marrow in multiple myeloma
Impact (as written by the applicant)	Development of an affordable cell therapy for multiple myeloma through improved production of anti-tumor macrophages generated from a renewable stem cell source
Major Proposed Activities (as written by the applicant)	• Define the functional impact of genetic IRF4 down-modulation on macrophage polarization status in primary and human iPSC-derived macrophages • Engineer M1-restricted human iPSC-derived macrophages deficient in IRF4 expression (IRF4KO-iPSC-MACs) • Functionally characterize human IRF4KO-iPSC-derived macrophages • Demonstrate improved anti-tumor cell activity of IRF4KO-iPSC-derived macrophages alone or in combination with antibody-mediated phagocytosis stimulation using human myeloma cell-based models • Demonstrate improved anti-tumor activity of IRF4KO-iPSC-derived macrophages alone or in combination with antibody-mediated phagocytosis stimulation in xenograft models of multiple myeloma
Statement of Benefit to California (as written by the applicant)	New and improved treatments for multiple myeloma will specifically benefit patients and their caregivers in California. As the iPSC-derived cell therapy being developed here could lead to a standardized, "off-the-shelf" cancer therapy, this approach could benefit individuals of diverse socio-economic backgrounds in our community by providing an improved treatment for a lower cost that will be appealing to hospitals as well as insurance companies (Medi-Cal, etc.) to better treat these patients.
Funds Requested	$1,425,600
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 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	2
Highest	75
Lowest	70
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 11	• Multiple myeloma is still an unmet medical need. iPSC-macrophages would be useful for treating different forms of cancer. • The proposed work will test iPSC-derived macrophages that are engineered to be locked in an M1 inflammatory state, as a way to treat multiple myeloma patients, which represent an important unmet medical need. • The PI provides exciting preliminary evidence in support of the main approach, which is to generate human iPSC-derived macrophages that are restricted in their polarization potential due to gene-targeted loss in IRF4 expression (IRF4KO-iPSC-MACs). • If these new therapeutic iPSC-derived cellular candidates are shown to be successful as per the proposed work, then there is a reasonable degree of likelihood that these findings will lead to new stem cell-based therapies to improve patient care. • iPSC-derived macrophages may exert anti-tumor activity and maintain a phenotype consistent with pro-inflammatory macrophages with genetic loss of IRF4 and the use of an iPSC source to derive the macrophages is an advance upon current cellular therapy with targeted macrophages. • The applicant plans to use GMP grade iPSC for making macrophage and also plans to test their cells' anti-myeloma efficacy in vivo.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 10	• The main rationale for the work is solidly based on preclinical studies that support to the notion of iPSC-derived macrophages homing to tumor sites and having an effect on the tumor microenvironment (TME). • iPSC-derived immune cells present an opportunity to develop reproducible cell products with multiple potential genetic manipulations. • The preliminary data are early stage but highlight the need for the proposed therapy for the treatment of multiple myeloma patients, who would benefit from better treatments. • Additional preliminary results in support of the shRNA or guideRNA to be used in the proposed work would have helped to de-risk the approach, and lend support to the generation of gene modified macrophages. • IRF4 downregulation decreases multiple myeloma cell survival. However, there is little preliminary data suggesting that IRF4 downregulation can skew a macrophage to M1 phenotype.
No: 2	• The preliminary data is not compelling. • The applicant has not shown their capability of performing CRISPR gene knockout in iPSCs. • The applicant did not show sufficient macrophage differentiation data across different batches. • The applicant did not provide preliminary data of iPSC-macrophage efficacy in vitro and in vivo.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 9	• This project is appropriately planned. • The experimental plan is sound. Investigators will develop IRF4-KO iPSCs and differentiate into macrophages. One potential pitfall is the unknown role of IRF4 in macrophage differentiation and an alternative approach of inducible knockdown of IRF4 has been suggested for mitigation. • Not many alternative approaches are described for all the aims. • This project seems like a four year project and may not be completed in two years.

No: 3	• The feasibility of the proposed work would be increased if the effectiveness of the shRNA lentiviral approach was demonstrated, which would significantly de-risk the proposed work using iPSCs. • Having identified a gRNA that works well to target IRF4 would increase the feasibility of the proposed work. • Milestone 3 and the subsequent milestones are dependent on the success of Milestone 2. • Milestone 4 will test whether the addition of anti-CD47 mAbs enhances IRF4KO-iPSC-MACs ability to phagocytose tumor cell lines. • A key aspect of Milestone 4 is testing whether IRF4KO-iPSC-MACs can differentially phagocytose normal B cells vs myeloma cells in the presence of antibodies. This would be an important efficacy and safety test of the IRF4KO-iPSC-MAC cell product. A more powerful test would be to have both normal and myeloma cells co-cultured with IRF4KO-iPSC-MACs and test the differential efferocytosis of the target cells. • The proposed work is well-structured, although whether an shRNA or CRISPR approach is the one to pursue confuses the main goal of the proposed work.
GWG Votes	**Is the proposal feasible?**
Yes: 4	*none*
No: 8	• Yes, the proposed aims are well structured and could be feasible within the outlined timeframe. • Although the milestones are clearly outlined, it is not clear whether sufficient de-risking of either approach, shRNA vs CRISPR/Cas9 has been done to increase the enthusiasm for the proposed work. • The feasibility is unclear without data on IRF4 knockdown skewing macrophage phenotypes, iPSC differentiation into macrophages, CRISPR-editing in iPSC, or iPSC differentiation with IRF4-KO. • Maybe, as the PI has enlisted a superb team with expertise in the generation of macrophages from iPSC to help with the translational aspects of the work. Nonetheless, showing some preliminary results would have increased the feasibility. • The applicant may not have all the skills to perform this project. • No preliminary data are shown raising concerns of feasibility.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 11	• Yes, the PI points out and addresses these factors in the proposal.
No: 1	*none*

Application #	DISC2-13524
Title (as written by the applicant)	Engineered injectable pre-vascularized microporous implants for neural stem cell transplantation after stroke
Research Objective (as written by the applicant)	We propose to develop an injectable soft material that can encapsulate brain cells and promote their long-term survival through blood perfusion to repair the brain after stroke
Impact (as written by the applicant)	If the proposed study is successfully achieved, we will have developed a nanotechnology-based stem cell therapy that enhances cell survival and integration in the brain after transplantation
Major Proposed Activities (as written by the applicant)	• Fabrication of the engineered material • Generation of the neural stem cells • Encapsulation of neural stem cells in the material and brain injection in the stroke lesion • Evaluation of brain inflammation and cell survival • Evaluation of vessel formation • Evaluation of tissue repair and recovery of neurological deficit
Statement of Benefit to California (as written by the applicant)	The proposed research will benefit the State of California and its large population with diverse ethnicity, gender, age, and socioeconomic status.
Funds Requested	$1,444,500
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 75

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

Mean	74
Median	75
Standard Deviation	3
Highest	77
Lowest	70
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 10	• The development of improved approaches to utilizing stem cell transplantation for the treatment of stroke addresses in important unmet medical need. • Enhancing survivability of delivered cells and greater nutrient access can be an important step to facilitating engraftment of injected cells. • Whether the proposed technology will be useful for the goals of the proposal is something that will not be evident for some time. • There is no information on time frames more aligned with the needs of treatment development.
No: 3	• Stroke is the leading cause of disability in the US and the third cause of death worldwide. To date, no clinical trials have succeeded in alleviating stroke survivors' neurological impairment. • This proposal focuses on biomaterials research, not stem cell technology. • A sufficient description for translation their technology into human clinical trials is needed.
GWG Votes	**Is the rationale sound?**
Yes: 7	• Increasing the survival of cells transplanted into the lesion site, which is a target of high levels of inflammation, would be very useful. • Poor vascularization of existing grafts also limits tissue integration in long-term survival. • The proposed project is rational, but it is not clear from the information provided whether it will actually work. The technical skills are clearly up to the task but there are no preliminary data providing proof of principle. • There are little or no preliminary data actually demonstrating that this approach will work in stroke transplantation models. • There are multiple steps that have not been carried out on that need to be successful in order for this to be a successful project. • Figure 8 provides data that indicates increased numbers of vessels and axons in the stroke cavity many weeks after brain transplantation. Thus, they do seem to be able to increase vascularization and the number of axons in the cavity. But it appears that these are not transplants that contain cells, which is the critical goal of this application. • The rationale is based more on intuition than necessarily preliminary data provided showing that their approach can work (even in vitro). The biomaterial is called pre-vascularized but there are not really functional vessel networks being delivered, though the ingredients may be assembled in situ. • More in vivo data is needed. What happens to these cells after transplantation? Do they become fully mature neurons?
No: 6	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 7	• The applicants have developed a novel biomaterial transplantation platform that appears to be useful in increasing survival of transplanted cells in injured brain. • That said, the transplants did not enhance functional recovery, cells did not survive past nine weeks, and neovascularization in the injected hydrogel was not observed. This has led them to propose to develop a pre-vascularized and immuno-modulating microporous platform that is designed to increase cell survival and vascularization of the transplanted hydrogel. • The studies are reasonably planned. Some more convincing data that the approach will work should be included. The other limitation is that the mouse model is really more an exclusionary model due to its size, in that if it does not work it will definitely not work in the human; if it works, the question will remain open and warrants moving to a larger animal model. • More alternative approaches are needed for Aim 3.
No: 6	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 9	• The preliminary data demonstrates the ability to perform all the proposed studies.

	• They have developed a technology that encourages vascular infiltration in the stroke cavity. They found this material increases vascularization at a few days after stroke. • Much of the work is based on evaluating what happens in the microporous biomaterial. As there are no data on what happens when you combine the neural stem cells with this approach, there is presently no indication whether there is a good probability or low probability of this project working. • These are ambitious aims. They showed that the biomaterial forms a microporous scaffold following transplantation. Once in place in the stroke cavity, these implants promote astrocyte integration in the scaffold and decrease microglia activity, although the basis for saying this is not clear.
No: 4	• May not be feasible to complete in two years. • Someone who is an expert in performing surgeries in mouse brain is needed for this team.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	• As stroke is a problem for all communities, this will, by definition, be useful for all communities. • Stroke impacts the general population including underrepresented individuals.
No: 0	*none*

Application #	DISC2-13458
Title (as written by the applicant)	An iPSC-derived neural progenitor cell product with inducible GDNF expression for treatment of ALS
Research Objective (as written by the applicant)	Induced Pluripotent Stem Cell (iPSC) - derived Neural Progenitor Cells (NPC) with inducible secretion of Glial Cell Line-Derived Neurotrophic Factor (GDNF)
Impact (as written by the applicant)	An iPSC-derived therapeutic candidate for neurodegenerative diseases, specifically; Amyotrophic Lateral Sclerosis, Parkinson's disease and Retinitis Pigmentosa.
Major Proposed Activities (as written by the applicant)	• Develop the inducible iNPC-GDNF cell lines • Differentiate, expand, and bank iNPCs from each clonal cell line • Establish an effective doxycycline dosing scheme in vivo • Test the efficacy of the inducible iNPC-GDNF cell-lines in the SOD1G93A rat model of ALS
Statement of Benefit to California (as written by the applicant)	ALS is a devastating disease that carries a large burden on the state's healthcare system (up to $300,000 in late stage). This therapy has the potential to lower the costs of care, but more importantly decrease suffering of Californians with ALS. The cell manufacturing and IND-enabling studies will be performed in California and therefore increasing state revenue, and supporting employment of Californians. Future trials would also be in California.
Funds Requested	$1,355,506
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 75

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

Mean	73
Median	75
Standard Deviation	3
Highest	75
Lowest	70
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 13	• Amyotrophic lateral sclerosis (ALS) is an incurable neuromuscular disease with progressive loss of motor neurons in the spinal cord and brain, leading to paralysis and death normally within 5 years of diagnosis. There are no effective treatments. • 90% of ALS cases have no known genetic lesion identified. As there are no treatments available, supportive therapy mediated by GDNF supplementation (via transplanted GDNF expressing cells) may yield some benefit and meet an unmet need. • Neural progenitor treatment for ALS patients without known mutations. No other treatment available. • Translational steps are clearly elucidated and apparent. This group also has previous experience with clinical trials related to a similar product of fetal central nervous system origin, which has as yet only just completed phase 1 trials. • Plans to move forward to FDA approval of trial. Similar product already in trial. • Essentially replaces an existing product with one derived from iPSC, aims to correct shortcomings of previous product.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 9	• Though ALS is caused by loss of motor neurons, these derive support from glial cell populations (astrocytes), which among other things, secrete protective GDNF. This grant is based on the rationale that supplying GDNF-expressing support cells may be an avenue for therapeutic intervention. • Another basis for this grant, which aims to make astrocytes that express GDNF in an inducible fashion from iPSCs, is the previous finding that astrocytes from fetal brain can alleviate some motor defects in a rat ALS model. • The main plan here is to engineer iPSCs to express GDNF when differentiated to astrocytes as a therapeutic that is renewable and free from the ethical concerns of the use of fetal brain tissue. • This group has already made induced neural progenitor cells (iNPCs). Using scRNAseq and immunofuorescence, they show that these are similar to previously developed NPCs of fetal origin. This group has also engineered iPSCs to contain constitutive and doxycycline-inducible GDNF expression, but the integrated constructs are not integrated into a silencing resistant locus and fail to express upon differentiation. • The PI proposes a combined cell and gene therapy approach based on the rationale that transplanting healthy astrocytes engineered to release the growth factor GDNF can act synergistically to preserve motor neuron survival and function. A similar product has already been studied in clinical trials. • The applicants rely on the success of a similar product in protecting motor neurons in animal, and its safe use in a phase 1/2a clinical trial for ALS. The similarities of fetal and iPSC-derived NPCs shown in the application are promising for iNPCs as a future therapy.
No: 4	• It is not clear whether the goal here is to deliver a specific trophic factor, achieve cell replacement, or both, and these mechanisms will not be sorted out by proposed study. • There is considerable preliminary data on a similar product. However, there are concerns about the formation of benign neuromas in the clinical trial likely associated with GDNF secretion, and it would be important at this stage to have some indication of potential clinical efficacy in the previous work.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 8	• The project is well thought out and shows the familiarity of the applicants with the subject. The goals are clear and appropriate. • The plan is to continue to develop and validate iPSC lines that harbor differentiation-protected expression of GDNF that can be differentiated to engraftable glial cells for therapeutic transplantation. • The project in iPSCs is essentially at its beginning: iPSCs need to be engineered to express constitutive and inducible GDNF, differentiated and confirmed to work, then validated by injection into the central nervous system of the rat ALS model.

	• The engineering approach may work, but is somewhat surprising given the recent successes of other engineering approaches.
No: 5	• The new design for induction of GDNF are interesting but not clearly elaborated. Reason for making the inducible lines is not clear; this section of the proposal was difficult to follow. • Will fate of human cells be assessed? • Benign tumors in trial of previous product a cause for concern particularly since there is no in-depth safety assessment in this study. How will levels of GDNF be controlled? No control for cells alone without GDNF induction?
GWG Votes	**Is the proposal feasible?**
Yes: 11	• Team has extensive experience in implementing very similar strategies. • Yes, though the iPSC engineering work is at its beginning. Unanticipated roadblocks could hinder the timeline.
No: 2	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 12	• Though ALS is most prevalent in non-hispanic white ethnicities, this group recognizes that non-white communities also suffer from ALS, yet have reduced access to healthcare. This group seems interested in extending therapies to underserved communities. • There is a commitment to support ALS therapies for diverse populations in California. • Addresses a fairly common condition with no good alternative therapeutic approaches.
No: 1	• The project design doesn't really consider the influence of these factors at this stage. However, the final product would probably benefit the whole population.

Application #	DISC2-13414
Title (as written by the applicant)	An interactive data resource for hypothesis testing in stem cell single-cell gene expression and validation of the results with brain organoids
Research Objective (as written by the applicant)	We are building a "virtual molecular microscope" where anyone can quickly visualize a very recent, high-throughput molecular assay, single-cell RNA-seq and spatial gene expression studies
Impact (as written by the applicant)	Currently, a lot of data has been published, hundreds of datasets on the cerebral cortex alone, but it takes hours to convert the datasets and look at them. Our websites will reduce this to seconds.
Major Proposed Activities (as written by the applicant)	• Find and convert existing single-cell gene activity datasets published over the last few years and add them to the website • Create the first "spatial" dataset of the cerebral cortex, one that shows gene activity in single cells but on sections of human brain tissue, not just the cells in isolation • Upgrade the website such that users can combine the data from Activity 1 (isolated cells) with Activity 2 (spatially arranged cells) and can compare the different datasets
Statement of Benefit to California (as written by the applicant)	California is a hub for stem cell research, partially thanks to CIRM. Our new data repository and data analysis tool will allow stem cell researchers, many of which who are based in California, to save a lot of time when looking at datasets. Our website will to share these datasets with the world. Finally, the project has the potential to attract more research funding from other sources to California. Hopefully, there will ultimately be health benefits to Californians thanks to this tool.
Funds Requested	$690,280
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 75

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

Mean	72
Median	75
Standard Deviation	6
Highest	80
Lowest	60
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 7	• Cortical organoids of the developing human brain are emerging tools to study normal and abnormal cell fates and the development of early neural lineages that would otherwise not be possible. Single-cell RNA-sequencing of organoids is especially useful due to their high cell variability. A open and cost free web-based database of all brain relevant sRNS seq datasets would enable scientists to correlate sRNA data with spatial resolution data • Animal studies in early brain development are limited by an absence of human specific cell pools - expanding our insight into human development using organoids is a field of increasing importance • Most sRNA seq data are generated by "desolving" the spatial resolution that is afforded by organoids. Thus the advantage of a 3D structure is lost by sRNA seq. Combining spatial resolution with sRNA seq would restore such information • The "usefulness" of the Cell Browser is currently measured by visits to the site without any other measure. A more unbiased and informative measure of usefulness should be introduced.
No: 6	• The application mentions some competitors. Together they contain at most 700 datasets. But at least 7000 single cell datasets exist, so this tool is needed. • This is a proposal to create a website with a set of computational visualization tools. The crux of our evaluation must then be to estimate how valuable these tools are. It is difficult to evaluate the potential utility of the proposed suite of web tools. I haven't used the site myself, so need to rely on the data in the proposal to judge the utility. These data are hard to evaluate. • The website would likely be useful. It is not clear whether the problem it solves is a bottleneck, or a less severe impediment to research. The "return on investment" is hard to judge for this proposal. • The project is vague regarding the application of the technology. • Impact is unclear. Existing databases have been used extensively. • Would like to see multiple letters of support from users. For this kind of proposal, such letters of support are critical. Would like to see some specific examples of how use of this database would lead to accelerated research (at the very least, theoretical examples, but could also be examples of research in other fields accelerated by similar databases, or an example worked up on a preliminary/rudimentary version of this database, and/or could also be based on simulations). • Letters of support can be from current users of existing tools (or beta versions) or potential users. • Figure 2. I don't see evidence for either the claim that usage drops in December or during summer vacation. Maybe a blip for August but probably not significant. Is it possible that some fraction of the unique users are bots or other "non-scientific-or-educational-use?". Perhaps statistics from a few "control" websites would be interesting, such as another new scientific site, a stale scientific site, and some non-scientific sites.
GWG Votes	**Is the rationale sound?**
Yes: 11	• The applicants focus on the cerebral cortex to achieve an in depth data base collection. This rationale is supported by observation that most human intellectual disabilities are associated with developmental changes during early embryonic brain development. • The proposal is built on a highly funded application that already successfully delivered a product. The extension of this work seem logical and well supported by an increased need to understand cell development in the early human brain. • Data published in 2020 show feasibility of generating relevant data in primary human tissue at various time points that are then juxtaposed to comparable cell populations in organoids. • Expanding the data set is important as not to bias data due to representation of data from a few dominant laboratories. • The overall plan is sound, and the outcome will be useful to the community. • Spatial transcriptomics is rapidly evolving and the platform may well be superceded.

	• Not clear what organoid data will be incorporated or why a particular organoid platform was chosen.
No: 2	• Not sure that organoid data would be particularly useful or stand the test of time.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 11	• The applicant has already shown a high degree of expertise to preform this kind of work and has chosen a suitable platform to extend the data set. The end product should provide an extensive easy to use data base that can be continuously expanded and updated. • Aim 1 seems to be a continuation of the original CIRM-funded application and should thus be part of the original application and should perhaps be eliminated from this application. • In addition, two other grants have the same goals as Aim 1. Not sure why the applicant does not see an overlap in funding. • Aim 2 and 3 generate new data and insight and are a true extension of the project. • The limitations of the project are not clear. • This is a capable bioinformatics team. • No pitfalls are discussed.
No: 2	• The proposal does not contain proof of concept experiments to demonstrate how the new tool will enable key advances in current state of the art and is therefore not fully responsive to the call
GWG Votes	**Is the proposal feasible?**
Yes: 12	• Very well-qualified group and the bioinformatics team produces great tools for the research community. • New preliminary data show targeted spatial transcriptomics on several dozen genes on two frozen sections of cortical tissue confirming feasibility. • PI effort is spread thin. A number of "other support" funding sources have less than 1% FTE allocated, with some as low as 0.12% FTE (2 hours per year).
No: 1	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 11	• Expanding genomics databases will likely help to achieve broader representation of underserved communities. • There are no obvious biases in the data proposed to be collated.
No: 2	• Not clear. There are no efforts made to include samples of undeserved communities.

Application #	DISC2-13522
Title (as written by the applicant)	A Novel Therapy for Sanfilippo B
Research Objective (as written by the applicant)	To develop a stem cell therapy for Sanfilippo B syndrome.
Impact (as written by the applicant)	There is no treatment for Sanfilippo syndrome, and other therapeutic approaches have failed in clinics. This proposal will develop a stem cell based therapy for Sanfilippo syndrome.
Major Proposed Activities (as written by the applicant)	• Generation of universal donor Embryonic Stem Cells (ESC) using state of the art genome editing technique. • Increase the level of the missing enzyme in universal donor ESC using state of the art genome editing technique. • Differentiate ESC into brain stem cells in vitro capable of secreting NAGLU (NAGLU-NPC). • Transplantation of NAGLU-NPC to evaluate if the cells can survive in the mouse brain and can repair brain tissue provide NAGLU enzyme. • Transplantation of NAGLU-NPC to evaluate if cells differentiate into functional neuron and integrate in the neuronal networks. • Transplantation of NAGLU-NPC to evaluate if cells can repair brain tissue and correct abnormal mouse behavior associated with Sanfilippo syndrome.
Statement of Benefit to California (as written by the applicant)	This application will help develop a stem cell therapy for Sanfilippo B disorder, a pediatric genetic disorder that currently has no treatment. If successful, this approach could be extended to several other lysosomal storage diseases, bringing a therapy for these catastrophic disorders.
Funds Requested	$1,426,350
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 73

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	73
Standard Deviation	4
Highest	80
Lowest	70
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 13	• This project, if successful may provide a new treatment option for Sanfilippo B and potentially other lysosomal storage disorders, for which at present, there is no effective treatment. • The proposal is a cell replacement therapy for lysosomal storage disease. Gene therapy or enzyme replacement have not yielded successful outcomes as yet. • There is great potential but at present, the impact is unknown since preliminary results involve only mouse ESC-derived neural progenitors cells. • It is not clear what exactly will happen next if the project is successful as the applicant did not provide possible options for progression from successful candidate discovery to translation. • There is no discussion on what the next steps would be if this project is successful (cGMP-compatible cell production, safety/toxicity studies, and so on).
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 11	• The scientific rationale for validating previous results by using human NPCs is sound and the preliminary data in a mouse model is compelling. • Cellular delivery of replacement therapy for a secreted product is attractive. • Strong preliminary data in mouse model, immuno-deprived mouse disease model generated. • The scientific rationale for validating strategy in the human systems is sound. However the rationale for using hypoimmunogenic ESCs is not as clear considering the brain is an immune-privileged site. In any case, if the PI thinks this is important, this should be compared to wild type ESCs. The same for the genetic modification to over-express NAGLU. There are just too many variables so if the results are not optimal, it will be difficult to understand the causes. • It is not clear why the applicant proposes to use a hypoimmunogenic model and what the relevant control is for that.
No: 2	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 4	*none*
No: 9	• The proposed project is a very interesting one, but in its current form is not well-defined nor constructed. • No rationale is provided for the genetic modification to overexpress NAGLU. Wild type cells should express NAGLU – do we need more than physiological levels? • The applicants should clearly explain how that will check/control that the right amount of enzyme is achieved - how will this be measured, as the Goldilocks effect is at play here? • No control of enzyme expression levels. • The applicant proposes use of hypoimmunogenic cells, but then overexpress NAGLU and uses GFP to label cells. Rigor is missing as important controls are missing. • The PI states ESCs are preferred to iPSCs since they are safer, but there is no acknowledgement to all the genetic modifications that will be applied here and no safety evaluation. • Potential toxic/harmful effects are not sufficiently well addressed. • Are HLA knockouts essential? What is the evidence and how will their reduced immunogenicity be assessed? • What will happen if the behavioral effects are positive but neuronal integration is not as expected, as has been shown previously (e.g. they are not necessarily co-dependent)? • Why is integration into neuronal circuitry significant and how will it be possible to tell whether this is necessary for any therapeutic effect?

	• Applicants do not address possibility that excess degradation of heparin sulphate proteoglycans might have toxic effects in CNS, these molecules have many important roles. Levels of production of enzyme should be controllable in some way, cell therapeutic should include suicide gene or other fail safe mechanism • Behavioral experiments are not clearly rationalized. • Too many interdependent aims, a delay at any stage could derail the timeframe of the project.
GWG Votes	**Is the proposal feasible?**
Yes: 7	*none*

No:
6
	• The proposed milestones and project outcomes are logical but unlikely to be achievable within the proposed timelines.
	• The timelines of different milestones are heavily overlapping and it is not clear how different objectives will be achieved.
	• Too ambitious for a two-year plan, the project could be simplified and still achieve its goal of proof-of-concept of the therapy.
	• From the description of behavioral tests and rationale for their choice, the team would benefit from inclusion of a team member with more experience in animal behavior.
	• Behavioral experiments are of particular concern - e.g. different tests are mentioned at different parts of this proposal, some tests are not correctly explained/chosen.
	  ◦ Novel object and social recognition is not the same as novel object/social interaction task - it is not clear what the applicant actually wants to test and why. What is the reason for believing that the mice will show increase in memory and learning performance?
	  ◦ The proposed social interaction test to evaluate if mutant mice show lower fear response is not an appropriate test for animals showing reduced fear response. There are other, much better suited tests, e.g. social approach-avoidance test; fear conditioning, using predator odors etc.
	• Feasibility is uncertain due to the introduction of many variables that are not controlled.
	• There are too many cell lines proposed.

GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 12	• Rare disease with devastating outcome and no treatment.
No: 1	• It is important to note that patients with such rare diseases are an undeserved community as pharma companies are largely not interested in those diseases. From that point of view, this proposal actually does serves the needs of undeserved communities. • This is not properly discussed. The applicant refers to the diversity in their own lab and the aspect of studying a rare disease.

Application #	DISC2-13478
Title (as written by the applicant)	ANCHOR for ART-SCID: All Non-Viral CRISPR-Cas Homology-directed Repair as First-in-Class Cure for Artemis-deficient Severe Combined Immunodeficiency
Research Objective (as written by the applicant)	All-nonviral CRISPR therapeutic for Artemis-deficient severe combined immunodeficiency
Impact (as written by the applicant)	Artemis-deficient severe combined immunodeficiency, overcoming current limitations of viral delivery for gene editing components
Major Proposed Activities (as written by the applicant)	• Establish feasibility of targeted integration of all-nonviral corrective transgene integration into a safe harbor in HSPCs • Demonstrate functionality of the transgene post-integration • Demonstrate repair of cellular defect in engineered ARTEMIS HSPCs and patient HSPCs • Demonstrate maintenance of HSPC stem cell properties post-integration • Perform a pilot safety assessment • Submit regulatory paperwork to the FDA to allow progression to the next stage of preclinical development.
Statement of Benefit to California (as written by the applicant)	We aim to eliminate a critical bottleneck on the path of gene-edited stem cell-based therapies to Californians with genetic blood diseases by developing a fundamentally new, broad-use, platform therapeutic approach. Our initial focus is on a severe disease that affects descendants of Navajo and Apache Native Americans. More broadly, our approach is expected to expand and accelerate California patient access to affordable CRISPR-based treatments for other blood diseases as well.
Funds Requested	$1,130,212
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 70

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

Mean	73
Median	70
Standard Deviation	6
Highest	85
Lowest	65
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	1
(1-84): Not recommended for funding	12

KEY QUESTIONS AND COMMENTS

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

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

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

Yes: 11	• This is a gene therapy (gene replacement) grant that aims to cure Artemis-deficient SCID (ART-SCID). This immunodeficiency disorder is caused by loss of the gene, and presents in infants and young adults.
	• This could result in an approach to correct the gene in ART-SCID hematopoietic stem and progenitor cells (HSPCs) for autologous corrective ex vivo gene therapy cures of ART-SCID patients.
	• CRISPR technologies could make gene therapies more likely to make it to market and the bedside.
	• It wasn't clear what we were reviewing or why we were reviewing it. This could have been made clear early in the proposal, and likely would have enabled the reviewers to all be on the same page.
	• There were a number of grantsmanship nuances that confused the panel. It would be best to lay these all out explicitly in the introduction so that we understand what is at stake.
	  • 1. Is this a grant to provide data to move to TRAN1? Might be most successful in that category, at least for CIRM. In which case, the grant should be focused on the product (HSPCs to treat ART-SCID), not the technology (ANCHOR).
	  • 2. Is this a technology grant? In this case the funding limit is lower, but it is unclear if any CIRM mechanism can support the amount of funding needed. Other funding mechanisms may need to be considered.
	  • 3. Is this a therapy grant? In which case ART-SCID has already been cured by lentiviral methods, so not novel.
	  • The above considerations may mean there is no excellent niche for funding from CIRM in currently open opportunities. Which is too bad, because this is really good science.
	• The advantages to CRISPR over lentivirus approaches should be made clearer. Maybe use bold text other other text highlights to make these sections of your proposal stand out more.
	• A good estimate of the the disease frequency is lacking. Estimate of "1/3000" appears to be based on a single article describing a case series of 5 patients. How many potential patients are there? How many can be recruited for this trial over what period of time? Has the frequency changed since the 1980 estimate, perhaps due to more outbreeding? What is the frequency and absolute number in other populations. Are the references for the disease frequency?
	• More discussion of alternative approaches is needed.

No: 1	• The functional preliminary data should be shown and not merely mentioned.
GWG Votes	**Is the rationale sound?**
Yes: 11	• The rationale is sound. The idea is to correct HSPCs from ART-SCID patients by introducing DCLRE1C into a safe harbor locus in HSPCs from patients. This type of approach has already been successful for other blood diseases. • Engineering of HSPCs is proposed using a non-viral CRISPR approach, which is somewhat novel, but as the engineering is ex vivo, it is not clear why there are advantages to using this over lentivirus approaches. • The applicant has developed a novel non-viral CRISPR editing system that would introduce corrective cDNAs into a safe-harbor locus. However, the preliminary data is mostly diagrammatic in nature, with only limited primary data. • The grant does not contain much preliminary data that goes beyond a description ANCHOR technology--there is little actual work with ART-SCID. • The grant doesn't contain any biological preliminary data that shows that introduction of DCLRE1C into deficient cells results in a functional correction, even in a cell culture system. • This project is technically sound but the applicant did not present sufficient and compelling data to support their project. No gene editing in HSCs was shown. • Critical preliminary data are not shown.

	• The inclusion of the AAVS1 safe harbor site in the preliminary data was confusing. The safety of that site has been known for years and is not novel. The proposal was written in such a way that the claim appeared to be a claim of novelty.
No: 1	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 9	• Some reviewers felt there were no (or very scant) pitfalls discussed. I suspect the synoptic form was not well appreciated by all reviewers (and may even have been missed). Therefore, I recommend a dense paragraph with lots of details about pitfalls. I like that actual pitfalls were included. It would have been a mistake to use the pitfall section to talk up the strengths of the team or be overly rosy and claim that that were no pitfalls. • Some reviewers felt that "No gene editing in HSCs was shown." So the description in the text and the letter of support was insufficient to show this. A figure would have been required to meet these reviewers' concerns. • More details were requested by some reviewers. This would be tricky given space considerations and the need to write a proposal that can be read by members of the committee that include non-scientists. However, since many of the reviewers are experts in stem cell biology, explicit details about how the stem cells are acquired / differentiated / assayed / manipulated would demonstrate expertise in these particular areas. • UNNECESSARY ACRONYMS (UAs) are not appreciated. e.g., targeted integration (TI). Also, define all acronyms (e.g., HSPC) the first time used in each section. • Note that the "Data Sharing Plan" is designed to discuss sharing with the broader world. Details of sharing data among your team do not belong in this section. • Detailed protocols and methods are going to be produced. Indeed, that is the main claim of the value of this proposal. But the only "data sharing" mentioned in the Data Sharing Plan is to publish results in the literature. Peer-reviewed literature publications seldom permit easy sharing of detailed protocols, nor are they always a prompt way to get protocols out to the broadest scientific community. The data sharing plans need to be expanded.
No: 3	• The actual research plan is in a very preliminary stage-mostly just a plan at this point. Therefore, there is considerable risk that a translation-ready product will not be in hand after a 2 year timeframe. • The grant does not contain very much in the way of primary preliminary data--most figures are diagrammatic in nature only. • The applicant did not present sufficient alternative approaches.
GWG Votes	**Is the proposal feasible?**
Yes: 8	• There was a sense this proposal was too ambitious in time frame and not enough budget to meet all the milestones. • Three key personnel are allocated between 1% and 5% FTE. This is not enough to do the work assigned to them. • Perhaps make the roles of appropriate personnel more prominent and increase their FTE. If the PI has direct experience in HSC gene editing, also make that clear. • It is recommended the applicant clearly and prominently outline the team's medical experience and access to patients. • It is important to draw attention to your successful ART-SCID trial with lentiviral manipulation. Perhaps a figure (not just text) would draw attention to these preliminary data. • This grant is at a very preliminary stage, is seems that achieving translation-ready milestones may be challenging.
No: 4	• The applicant may not achieve their proposed milestones within two years because of potential difficulties in editing primary HSCs and also expansion of primary HSCs. • This team will be stronger if they include experts in HSC biology and gene editing. They may need to collaborate with doctors to isolate human HSCs.
GWG Votes	**Does the project serve the needs of underserved communities?**

Yes: 12	• ART-SCID disproportionately affects descendants of Navajo and Apache Native Americans in the Southwestern United States, where homozygosity causes SCID in 1/3000 to 1/4000 births, which is the highest incidence of SCID in any human population. • ART-SCID is most common in Navaho and Apache ethnicities, and the applicants correctly note that it is harder to find matched autologous sources of cells for patients of non-white origin.
No: 0	*none*

Application #	DISC2-13495
Title (as written by the applicant)	Investigate vision protection after subretinal injection of a combined cell and gene product at the clinically relevant stage of retinal degeneration
Research Objective (as written by the applicant)	A combined neural progenitor cell and gene product: human neural progenitor cells engineered to release glial cell line-derived neurotrophic factor (hNPC-GDNF)
Impact (as written by the applicant)	The combined neural progenitor cells engineered to release GDNF. hNPC-GDNF will be used to treat retinitis pigmentosa, regardless of mutations, and will improve the quality of patients' lives.
Major Proposed Activities (as written by the applicant)	• 1) Culture hNPC-GDNF and hNPC, store enough cells for experiments 2) To investigate whether hNPC-GDNF offer better vision protection than hNPC following subretinal injections in a rat model of RP • 1) hNPC-GDNF secrete therapeutic amount of GDNF 2) Confirm donor cell survival; hNPC-GDNF offer significantly better efficacy than hNPC • 1) Long-term efficacy after subretinal injections of hNPC-GDNF at stage II of RP 2) Check inflammation-related response from cell-and control treated eyes by immunohistochemistry and ELISA • Start dose escalation study with a range of doses; identify the optimal dose for future IND enabling study • Subretinal injections of labeled hNPC-GDNF or control into the dorsal-temporal and-nasal parts of the eye. Perform functional tests to confirm efficacy before termination. • Sample collection and processing for a single cell RNAseq and transcriptomic analysis. Identify top regulated genes and proteins from both injected cells and host retina over time.
Statement of Benefit to California (as written by the applicant)	Our approach of transplanting hNPC-GDNF to slow down retinal degeneration is broadly applicable, which fits perfectly for the diverse California population, including underserved racial/ethnic communities. The approach avoids many of the immunological complications of allogenic transplantation by targeting immune privileged eye. Providing trophic factor GNDF along with neural progenitor cells is an approach that is applicable to all patients, regardless of race, sex and ethnicity.
Funds Requested	$1,357,802
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 70

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

Mean	71
Median	70
Standard Deviation	3
Highest	80
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0

(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 9	• The previous major concern of addressing the ongoing CIRM-funded clinical stage related award has not been addressed. One milestone out of five have been completed. • The project is in phase 1 clinical trial with a budget of over $10M. • The need for the proposed study is not clear. An ongoing clinical trial is underway and supported but delayed. There, un-modified neural progenitor cells are used. Is the goal to modify the existing ongoing clinical trial? It is not clear whether the preclinial study proposed here is critical to alter the existing trial or is geared toward a new trial assuming the existing trial will fail? • The applicant mentioned a clinical trial. It is not clear whether this is the same trial that was awarded by CIRM. This award is not limited to test safety and tolerability but is geared towards "assessing safety and efficacy of subretinal injection of human neural progenitor cells for the treatment of retinitis pigmentosa". There are no comments regarding efficacy which is confusing.
No: 6	• Retinitis pigmentosa is an important problem. The rat model may not be the best to capture the challenges of injected cell viability in the human eye. The current proposal seems to suggest that an ongoing clinical trial using non-genetically altered cells alone will fail by the insufficient secretion of GDNF. There is no real data to support this contention. • General relevance to retinitis pigmentosa is claimed but isn't supported by data.
GWG Votes	**Is the rationale sound?**
Yes: 8	• Engineered cells seem to have a higher efficacy. Preclinial studies already published in 2007 show that of GDNF expressing human neural progenitor cells (hNPCs) offers dramatic photoreceptor protection. This begs the question of why the funded clinical trial did not use engineered cells. What was the rationale for that and why is this rationale now outdated? • The injection timing is highly relevant for the human therapy (onset of vision loss).
No: 7	• Neuroprotection using a single therapeutic, GDNF, is unlikely to to produce clinically significant functional benefits in humans. • Neuroprotective agents may improve survivability but may not address the root cause of the problem. The proposed approach could be used as an adjunctive therapy.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 7	• There is plenty of preliminary data suggesting that the proposed studies can be completed without any issues. • The potential differentiation of NPC into other cells upon transplantation at later time points is not addressed. • Aim 3 seems premature. At this time, it is not clear how NPC behave post transplantation. Labeling cells and following their fate over time seems to be necessary first step. The needs for costly single cell RNA sequencing and spatial transcriptomic analysis is not well rationalized. • The concern of ongoing GDNF delivery is not directly addressed. • The significance of the amount of photoreceptor preservation is not clear in light of no change in visual acuity.

No: 8	• The proposal is unambitious, and in the context of the ongoing trial clinical trial, is somewhat retrograde. Do the applicants predict that their clinical trial will fail?
GWG Votes	**Is the proposal feasible?**
Yes: 12	• The team is well versed in GDNF biochemistry, NPC manufacture and use of the rat model. • Considering that there are a couple of clinical trials using cells alone (eye) and engineered cells (ALS), there is sufficient safety profile to study the current cell therapy for retinitis pigmentosa without necessarily optimizing in the rat. In this regard, the proposal could be more ambitious.
No: 3	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 14	• The disease is associated with poorer mental health and disparities in eye care access disproportionately affects underserved populations. • Retinitis pigmentosa can impact the general community including underrepresented individuals.
No: 1	*none*

Application #	DISC2-13437
Title (as written by the applicant)	A small molecule therapeutic to differentiate cancer stem cells
Research Objective (as written by the applicant)	We will develop a small molecule that blocks the growth of human pancreatic cancer and triple negative breast cancer stem cells in vitro and in vivo.
Impact (as written by the applicant)	This work will lead to a new treatment for cancer stem cell driven diseases such as triple negative breast cancer and pancreatic cancer, and it will improve patient prognosis and stratification.
Major Proposed Activities (as written by the applicant)	• Identify Additional Hits: 1) Screen a library of compounds that are analogs of current hit; 2) Screen hits for co-treatment potential with standard chemotherapies • Identify & Characterize Lead Compound: 1) Conduct in vitro metabolic stability studies; 2) Conduct in vivo PK studies; 3) Choose and validate identity and purity of lead compound • Validate Lead Efficacy In Vivo: 1) Prepare Patient-Derived Orthotopic Xenograft Models; 2) Test efficacy of lead compound and co-treatment strategies • Characterize the Mechanism of Action of Lead Compound: 1) Identify signal transduction pathways; 2) Identify protein-binding targets
Statement of Benefit to California (as written by the applicant)	Triple negative breast cancer and pancreatic cancer are prevalent in the State of California. Because this research will lead to development of new treatments for these diseases, the citizens of California will directly benefit. Pancreatic cancer and triple negative breast cancer affects people of all ethnicities and socio-economic status. Thus, if successful, the new therapeutic will improve outcomes for patients throughout the State of California.
Funds Requested	$1,425,600
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 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	3
Highest	75
Lowest	60
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 11	• Cancer stem cells represent a major challenge for cancer treatment as these cells are tumor-initiating, lead to metastases, and are resistant to chemotherapy. Elimination of cancer stem cells through differentiation would be a significant step forward in cancer treatment. • If successful, this product could be very impactful for cell differentiation.
No: 1	• Developing improved ways of getting rid of cancer stem cells could be useful in cancer treatment. • The potential for impact is impossible to evaluate as there are no preliminary data.
GWG Votes	**Is the rationale sound?**
Yes: 9	• The treatment leads to inhibition of tumor growth and a higher frequency of cells with increased expression of a marker suggesting differentiation. • The proposed pathway markers are increased in stem-like tumor cells and the gene signature can predict poor outcomes in several tumor types. Therefore, inhibition of these pathways may improve anti-tumor responses. • Rationale is sound but could use more preliminary data demonstrating the on-target effects of some candidates in vivo.
No: 3	• Data on the molecule from previous studies suggest that it's reasonable to try this approach. Whether there will be any new derivatives of interest is unknown. • Would like to see more preliminary data. • There are no preliminary data.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 7	• Good plans, but very ambitious. More preliminary data is essential to de-risk the proposal. • The investigator will computationally screen a library of millions of compounds for those structurally similar to the drug and then for function against cell lines in vitro and in vivo. This is a sound methodology. However, the rationale for not moving forward with the drug is not clear.
No: 5	• The drug that they are studying was developed by somebody else, and so are the analogues of this drug. They also will be carrying out a fee-for-service screen as a virtual screen. Thus, there is a long road from the identification of compounds of potential interest to data on utility.
GWG Votes	**Is the proposal feasible?**
Yes: 6	• The proposal is over ambitious, each milestone could be its own grant. • Unclear feasibility based on absence of preliminary data. • Most data included shows proof of concept, but each milestone is ambitious with unclear feasibility.
No: 6	• The milestones and outcomes are logical. Whether or not they will be achieved as proposed is impossible to tell. • The aims are too ambitious for a 2-year project. Each of the last four aims are independent projects that can take 2 years. • The major risk for feasibility is the discovery of other compounds similar to the drug that will have activity.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 12	• A small molecule that differentiates cancer stem cells would be impactful for all communities because it would increase the efficacy of chemotherapies. • Cancer does not select for differences in these parameters. • The project serve the needs of underserved communities.
No: 0	*none*

Application #	DISC2-13455
Title (as written by the applicant)	Development of small molecules to restore function in neurons from Intellectual Disability Syndromes
Research Objective (as written by the applicant)	We use human induced pluripotent stem cell derived neurons from patients suffering from Rett Syndrome. We discover molecules that restore function in Rett neurons by blocking cellular senescence.
Impact (as written by the applicant)	These novel compounds will treat Rett Syndrome, and potentially any other Intellectual Disability Syndrome where neurons suffer from premature senescence
Major Proposed Activities (as written by the applicant)	• Generate small molecules with the ability to block neuronal senescence and enter the brain. We currently have 55 molecules, we will synthesize at least 50 additional analogues. • We will perform activity assays in vivo as well as determine which molecules are most likely viable clinical drugs. • We will determine the mechanism of action of our best molecules to understand how they work to restore function in Rett neurons. • We will work with our clinical partner to determine best practices for potential formulation and delivery of molecules, as well as identify appropriate patient populations.
Statement of Benefit to California (as written by the applicant)	The project described here will bring great benefit from families suffering with Rett Syndrome. Our novel small molecules will be translated into drugs that have been shown to ameliorate symptoms of Rett Syndrome in neurons through modeling via human induced pluripotent stem cells. Rett Syndrome strikes 1:10000 live female births, so in state like California, this means thousands of families are suffering right now, with no treatment options available.
Funds Requested	$1,306,000
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 70

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

Mean	70
Median	70
Standard Deviation	4
Highest	75
Lowest	65
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 8	• The project remains highly significant and there is currently no cure for Rett syndrome and also intellectual disability syndromes. • The conceptual framework of addressing cellular senescence provides a potential pathway to an entire array off disorders. • The applicant states that "... we have evidence that disease in a dish models for other Intellectual Disability Syndromes such as KAT6, CDKL5, Boring-Opitz etc. all show signs of neuronal senescence in vitro". There are no data provided to substantiate that claim.
No: 4	• The authors note that many Intellectual Disability (ID) diseases have senescence defects. The diseases listed are VERY different from one another and result from very different genetic mutations. Global increase in dendritic branching in the brain seems like a very non-specific approach to treat all ID syndromes. • Translation seems very far away. • The potential impact may be low, as the proposed drugs did not have any clear-cut effects in vivo. • There were little effects of the proposed drug candidates and the senescence hypothesis for understanding developmental disorders remains largely untested. That's not to say that it's an un-interesting hypothesis, but the data supporting it are limited.
GWG Votes	**Is the rationale sound?**
Yes: 6	• The focus on dendritic branching defects as being a relevant readout in ID syndromes is well-supported by data in organoid cultures and seems to be a reasonable endpoint. • The causal relationship between reduced dendritic branching and senescence is still not clear. Is defective dendritic branching leading to neuronal senescence or is a program of neuronal senescence leading to dendritic branching defects? Addressing correlation versus causation will be important to design the exact timing of a therapeutic intervention. • Figure 11 is unclear. Pre-treatment of cells with subsequent induction of damage seems clinically irrelevant. Why are cells not treated after irradiation?
No: 6	• Preliminary data, as noted in the previous review, is weak and incomplete. For example, Fig. 16 lacks sufficient data to interpret what is being shown. • As in the first review, there are issues with the preliminary data. For example, the PI states (Fig. 14) that compound 26 has a modest effect on seizures in mice. From the data, this does not appear to be true. In addition, no information is given regarding how the experiment has been performed, or what was measured. • The lead compound seems to make things worse in respect to four of the assays shown; the new derivative makes things better to a notable extent in one of these assays. None of the compounds show any effects on seizures.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 3	*none*
No: 9	• It is unclear if a candidate will be developed that will help patients. • The goal is to reverse ID. However, it is unclear when the hypothetical treatment would be given. Brain development is highly complex. There is no discussion if the treatment will be provided to kids and/or adults, though data in the literature suggests that treatment would need to be continuous throughout life. • The applicant states that "the ID Syndrome lines we have tested show evidence of neuronal senescence (Figure 5 and 6)." However, Fig. 5 and 6 only show Rett iPSC. This is confusing. • The applicant states that it makes sense only to focus on females due to the severity in males. However the description of the mouse experiments include males and females and in fact the applicant points out that males will be used to show efficacy of drugs due to their severe phenotype - the inclusion of sex as a variable in the proposal is thus very confusing.

	• The revised application still does not include experiments that would test anti senescence drugs developed by others in their model of Rett Syndrome. Not having a baseline of the efficiency of existing drugs limits the significance of the proposal. It would be important to show that the drugs developed here are superior to existing approaches. • It is a concern that the deficiencies in the data do not raise any questions about whether or not the core hypothesis is valid. It is particularly disturbing that the lack of support of in vivo data is not considered in terms of pitfalls and alternative approaches. • No alternative experiments are proposed.
GWG Votes	**Is the proposal feasible?**
Yes: 8	• Utilizing the reversed Rett sponsored program is a clear strength of the proposal. • Timeline not updated from previous submission (has 2021 dates). • In general, it is not clear how the numerous co-PI's at 1-2% effort will be able to oversee staff (at 50-100% effort). It will take much more than 1% of a co-PI's time to supervise a 100% postdoc. • No pitfall discussion is provided.
No: 4	• The odds of this project yielding something ready for translation seem very low. • There is very little information in this regard. This is a very difficult problem for diseases like this, because the rate of progression between individuals varies enormously. Thus, how would you know whether a drug worked in an actual clinical setting? Only if their endpoint of actual reversal was achieved. This critical question is not addressed.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 12	• Rett syndrome is associated with considerable costs to families and patients a small drug treatment that can impact the disease would make an enormous difference to families with limited or no resources. • Only female patients will be served (males do not usually survive birth). • Genetic diseases do not discriminate between different ethnic groups.
No: 0	*none*

Application #	DISC2-13541
Title (as written by the applicant)	Developing anti-SEMA4D antibody drug conjugate as a prophylactic therapy for brain metastasis
Research Objective (as written by the applicant)	We will develop a novel targeted prophylactic therapy to prevent brain metastasis by using antibody drug conjugate targeting a cell surface receptor that promote cancer stem cells to get into brain.
Impact (as written by the applicant)	This therapeutic development will fulfill the unmet need for preventing brain metastasis, which is a devastating complication for many solid tumor types with limited therapeutic options.
Major Proposed Activities (as written by the applicant)	• Generate human monoclonal antibodies to SEMA4D and select 1-2 lead candidates that can be internalized efficiently by SEMA4D expressing cancer cells • Generate anti-SEMA4D ADCs with excellent stability, affinity, and specificity • Evaluate the efficacy and identify dose window using cancer cell lines and normal cells with different level of SEMA4D • Quantify pharmacokinetics for the lead anti-SEMA4D ADC in mice • Assess the efficacy of the lead anti-SEMA4D ADC in cancer xenograft model
Statement of Benefit to California (as written by the applicant)	Brain metastasis is the most common intracranial malignancy with rising incidences and devastating prognosis. The prognosis of many cancer types influenced by the racial background, with underserved racial/ethnic groups having a higher brain metastasis rate. Therefore, our planned development will address a crucial need for patients with the aggressive cancer subtypes, commonly enriched in the underserved racial communities that constitute a significant patient population in California.
Funds Requested	$1,417,700
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 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	69
Median	70
Standard Deviation	5
Highest	80
Lowest	55
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 9	• Brain metastasis (BM) of cancer is a common consequence of advanced stage of cancer, and poses a significant clinical challenge because of difficulty to treat. The PI proposes to develop a novel strategy to prevent, rather than treat, BM, which might be an ideal and rational approach to reduce BM-related morbidity and mortality. • Blocking cancer stem cells from crossing BBB could be very significant.
No: 4	• This grant may alleviate metastasis in breast cancer by targeting cancer stem cells with an antibody. • This grant seeks to prevent cancer stem cells (CSCs) from crossing the blood brain barrier (BBB) using an inhibitory antibody drug conjugate (ADC) directed against the SEMA4D protein, discovered by this group. This could prevent metastasis to the brain.
GWG Votes	**Is the rationale sound?**
Yes: 7	• The notion is that inhibition SEMA4D with antibodies may lead to a therapy to alleviate metastasis to the brain. • This group found a receptor (SEMA4D) that is expressed on brain cancer cells in one patient that has been shown to be important for CSCs expressing this antigen to cross the BBB. Inhibition SEMA4D with antibodies may lead to a therapy to alleviate metastasis propensity beyond the brain. • The rationale is sound but it is unclear whether antibody blockade alone will be enough to limit migration across BBB. What about chemokine receptors, selectins, integrins, ICAMs?
No: 6	• Since SEMA4D is expressed on the cell surface of CSCs, it is a rational approach to target SEMA4D by anti-SEMA4D ADC and kill CSCs and tumors that express SEMA4D. • The PI mentioned that some normal cells express SEMA4D. There is a potential that anti-SEMA4D-ADC can have significant normal tissue toxicity. • Rationale is not well-supported by data, off target toxicity needs to be discussed.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 7	• The proposal will address important questions and proposes milestones that are needed for preclinical translational development of systemically administered therapeutic molecules. • Good plans in place but concerns regarding off-target toxicity that is largely not addressed. SEMA4D is expressed on activated T cells which cross the BBB. Eliminating these cells could be deleterious.
No: 6	• The in vivo aspect of this research is fairly weak. They propose to simply inject CSCs into peripheral blood, then see if the therapeutic ADC will inhibit these. This approach does not involve the BBB, which is central to that goal of this approach (to inhibit CSCs from crossing the BBB). • The research plan has some design problems, most notably, the in vivo assays do not really model brain cancer and metastasis. • This group need to make antibodies, then conjugate them to a toxin, then test them for efficacy, so this may take well beyond the 2 year timeframe.
GWG Votes	**Is the proposal feasible?**
Yes: 5	• Proposal is ambitious but feasible.
No: 8	• The PI mentioned that the team aims to establish anti-SEMA4D antibodies that selectively bind membrane bound SEMA4D, but spare soluble SEMA4D. It is very uncertain if this can be achieved. And if not, it is unclear how circulating soluble SEMA4D might impact the efficacy of this anti-cancer strategy.
GWG Votes	**Does the project serve the needs of underserved communities?**

Yes: 12	• There is evidence that cancer BM disproportionally impacts the underserved populations, and this research proposal has a potential to address patients from underserved communities. • The project serve the needs of underserved communities.
No: 1	*none*

Application #	DISC2-13432
Title (as written by the applicant)	Human Induced Pluripotent Stem Cell-Derived Endothelial Cells for Treatment of Peripheral Arterial Disease
Research Objective (as written by the applicant)	We propose the delivery of human induced pluripotent stem cell-derived endothelial cells (iPSC-ECs) for treatment of peripheral arterial disease.
Impact (as written by the applicant)	A critical need in peripheral arterial disease is a therapeutic that augments blood perfusion to the ischemic limb. iPSC-ECs are intended to restore blood perfusion and revascularization to the limb.
Major Proposed Activities (as written by the applicant)	• To generate human iPSC-ECs from donor cell lines and characterize the cells for endothelial phenotype and function • To assess the efficacy of human iPSC-ECs for treatment of peripheral arterial disease (PAD) in a murine model • To evaluate the safety and biodistribution of iPSC-ECs from donor lines in a mouse model of PAD • To identify biomarkers that predict responders of iPSC-ECs therapy • To develop alternative strategy to co-deliver iPSC-ECs with injectable collagen microspheres for enhancing cell survival in a mouse model of PAD • To generate the Target Product Profile
Statement of Benefit to California (as written by the applicant)	This stem cell-based therapy will benefit California by providing a new treatment for peripheral arterial disease (PAD), which is a prevalent cardiovascular disease. Production of these therapeutic cells at the clinical scale will provide job opportunities to citizens of California. The benefits of this new regenerative therapy will have a tremendous impact on the state of California and to patients suffering from PAD.
Funds Requested	$1,043,000
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 70

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

Mean	68
Median	70
Standard Deviation	7
Highest	80
Lowest	60
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 12	• The proposal focuses on an important disease. Current treatment options are limited. • A central feature of PAD is dysfunction or damage to the vascular endothelial cells (ECs) that line the inner layer of blood vessels. Methods to restore a healthy endothelium by enhancing angiogenesis in response to limb ischemia hold promise for the treatment of PAD. Endothelial progenitor cells derived from diseased patients are reduced in replicative and functional capacity and there is a need for an alternative therapeutic source for cell therapy. • PAD is a very important target. • The proposed therapeutic approach can transform the field of cell therapy for treatment of PAD, shifting away from conventional adult stem cells to the transplantation of iPSC-ECs, which can be generated in unlimited quantities in a patient-specific manner. • The applicants have demonstrated the ability to get efficient numbers of iPSC-ECs with high purity. Studies spanning in vitro EC phenotype characterization, mouse subcutaneous capillary formation, and then efficacy in a mouse model of limb ischemia are proposed. The limitation is the efforts need to be evaluated in a large preclinical animal model. In this regard, the proposed study is a bit incremental. • There are numerous concerns related to the proposed experiments which make it unlikely that the proposed experiments will develop a successful cell based therapy. There is limited progression and evidence that the proposed experiments can progress to translation.
No: 3	*none*
GWG Votes	**Is the rationale sound?**
Yes: 9	• The rationale to deliver ECs to ischemic tissues is a strong one that is supported by their preliminary data. • The applicants list a publication which was published quite a few years ago demonstrating the effect of using hiPSC-ECs for the treatment of peripheral artery disease. The initial evidence is suggestive and very preliminary. • Numerous aspects of the proposal lack sufficient preliminary evidence. • There is not sufficient preliminary data for the proposed milestone of identifying biomarkers. • There is no justification or preliminary data supporting the selection of multiple lines and the criteria for how these lines are selected.
No: 6	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 5	• Difficult to judge- no description • The proposal is logical but the focus on in vivo mouse model (small animal) is a major limitation to clinical translation of their approach considering the concepts underlying the proposal are borne out in murine models that are nearly a decade old. • The basis for the study stem from 2 papers from the team that are greater than 10 years old. While the data is strong, the field is much more advanced and the novelty of the current approach is diminished. The focus on the underperforming IPSC-ECs to test with collagen microspheres suggests that in the current mouse model, IPSC-ECs that are well performing are sufficiently good to treat the ischemia. • As such, the approach needs to transition to a larger animal model where the scale of size (toward human) is considered.

No: 10	• There are numerous concerns related to the design of the project:
	  ◦ There is no justification for the number of lines.
	  ◦ There is no preliminary data or justification which would suggest that the proposed biomarker and proteomics study can identify markers of treatment success. The proposed sampling of samples for RNA sequencing lacks detail and it is likely that underlying sampling variability will be the dominating factor.

	● There is no preliminary data supporting the concept that using collagen microspheres will have a beneficial effect. And if it is truly beneficial, then this questions the experiments for the previous milestones. Why not used the best possible method? There is no rationale why the investigators use iPSC-ECs with potentially low efficacy. Why would one not try to maximize therapeutic efficacy? ● Some concerns are discussed. Immunogenicity will be a major concern for the translation to humans. ● The proposal is ambitious.
GWG Votes	**Is the proposal feasible?**
Yes: 10	● The preliminary data is strong - based largely on prior publications. ● The experiments can be conducted in the proposed timeline. ● The team appears to be qualified, resources sufficient, and budget appropriate. ● Timeline may be optimistic.
No: 5	● Time line seems to be insufficient.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	● Including minorities in study cell lines is exemplary. ● iPSC-ECs will be derived from a diverse population of patients. ● The disease under investigation is of relevance for the diverse California population. ● It is unclear whether the proposal addresses race, ethnicity, sex and gender diversity.
No: 2	*none*

Application #	DISC2-13535
Title (as written by the applicant)	Targeting glioblastoma using human pluripotent stem cell-derived neural or glial progenitor cells loaded with oncolytic virus
Research Objective (as written by the applicant)	The object of the study is to develop a novel human induced pluripotent stem cell (iPSC)-based therapy for effective treatment of glioblastoma by loading iPSC-derived neural or glial progenitor cells with oncolytic virus.
Impact (as written by the applicant)	Combining human iPSC-derived progenitor cells with oncolytic virus could allow us to develop an effective therapeutic strategy against glioblastoma, the deadliest primary brain tumor.
Major Proposed Activities (as written by the applicant)	• Generation of human iPSC-derived neural progenitor cells (NPCs) or glial progenitor cells (GPCs) • Loading oncolytic virus into NPCs or GPCs and characterizing the resultant cells • Testing the effect of oncolytic virus-loaded NPCs or GPCs on glioblastoma cell survival in vitro • Testing the effect of oncolytic virus-loaded NPCs or GPCs on glioblastoma progression in vivo
Statement of Benefit to California (as written by the applicant)	Glioblastoma is the most deadly primary brain tumor with no cure. California is estimated to have ~12% of all cases of glioblastoma in the U.S. In addition to the emotional and physical pain glioblastoma inflicts on families, it produces a huge medical and fiscal burden on California. Thus, there is a real need to develop an effective strategy of treatment for this disease. We propose to address this need by establishing an effective human iPSC-based oncolytic viral therapy for glioblastoma.
Funds Requested	$1,358,100
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 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	85
Lowest	60
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	1
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 10	• There is an urgent need in neuro-oncology for alternate treatment approaches for glioblastoma. The proposed technology will result in a new neural/glial progenitor cell carrier for a novel oncolytic virus that will be developed for glioblastoma treatment. • Despite great efforts in therapeutic development, median survival for glioblastoma patients is only about 12 to 18 months. Therefore there is an unmet need to find a cure for glioblastoma. This proposal addresses the unique unmet need. However, the technology described in this proposal falls short of developing an effective therapy for such tumors. • The proposed studies use human iPSC-derived neural progenitor cells (NPCs) to deliver oncolytic poxvirus CF17 intratumorally in glioblastoma patients. Given that >80 of glioblastoma undergo tumor bulking and subsequent treatment with chemotherapy and/or radiotherapy, the proposal does not address how their technology could be integrated initially into standard of care or ultimately as a "stand alone" therapy. • The proposal includes a well laid out plan for the creation of NPCs, viral loading, and thorough in vivo experiments. However, there is insufficient consideration given to the immune aspect of oncolytic virus mediated cell death in pre-clinical studies. • Glioblastoma needs new therapies. Oncolytic viruses provide one such approach. • Unfortunately, this project is not likely to generate an effective product.
No: 4	*none*
GWG Votes	**Is the rationale sound?**
Yes: 7	• Yes. This proposal aims to develop an oncolytic viral therapy as a superior approach to treat glioblastoma. In their approach, loading oncolytic virus into tumor-trophic progenitor cells is intended to improve both efficacy and immune evasion. • Yes. The project is soundly based on: 1) the potential for oncolytic viruses to provide direct tumor cell killing through preferential replication in neoplastic cells, 2) the potential for oncolytic viruses to stimulate anti-tumor immune response, 3) the utility of stem/progenitor cell carriers to protect newly produced viruses from premature immune clearance and, 4) the utility of stem/progenitor cell carriers to home to disseminated sites of tumor. • The preliminary data are supportive of the applicant's ability to generate the desired neural/glial progenitors and to load them with virus. They are further indicative of an up and running intracranial implant model in which anti-tumor activity can be quantified via bioluminescence imaging. Finally, they are supportive of the array of evaluate techniques to monitor cytotoxicity and migration in vitro, as well as cell and virus tracking in vivo. • The focus on a novel carrier like glial progenitor cells and on a novel virus like the combinatorial orthopoxvirus are soundly based on the premise that improved efficacy (compared to prior reagents) might be possible with greater efficiency of viral delivery and greater virally-mediated cytotoxicity. Finally, the plan to use a single source of neural stem cells for all patients is soundly based on the time and cost involved in generating patient-specific reagents. • Less sound elements of the proposal are the expectation that neuronal/glial progenitor cells will remain undifferentiated as they travel to sites of cancer pathology. It is known that these cells tend to differentiate into glia. This is important as glia will not remain "invisible" to the immune system, or may persist in a patient. The applicant needs more information about the potential fates of these cells. • The applicant focuses on the sex of the neoplastic cells to address sex as a biological variant. Immune cell activity, including microglia function, are well-known to exhibit substantial sex differences. Any in vitro and in vivo measures of microglial function should be tested independently with male and female microglia. • The project plan does not include a rigorous evaluation of the long-term effects in patients of this novel combination of cellular carriers and virus. The survival curves of transduced progenitor cells suggest that there may be some long-lived virus-producing cells. These cells will be competent to migrate throughout the CNS and differentiate, and may be a safety risk.
No: 7	• Unfortunately, the integration of this product into the standard of care is not considered.

	• Neural progenitor cells as carriers may be problematic as they tend to differentiate into glia and become "visible" to the immune system. The applicant should discuss this potential pitfall. • I wanted to see a discussion of potential off-target effects. There is no discussion of off-target effects other than a reference to a paper from 2015. There are many recent papers on the subject. The issue of off-target effects is not resolved and merits discussion. • The applicant claims that oncolytic virus is unaffected by tumor evasion. However, it's also possible that oncolytic viruses have not been in development long enough for investigators to report or identify tumor evasion in their studies. • The planned studies will not be conducted in a clinically relevant model.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 5	• The project is well designed to meet the expected outcome, but questions related to cell migration and translation into the clinic remain.

No:
9
	• The project is appropriately designed to further develop the novel carrier/virus reagent. However, there are a several weaknesses in the design of efficacy and toxicity studies.
	  ◦ The tumor implantation model approach has several weaknesses. The location of implantation (stereotactic coordinates) is not presented. It should be, along with a rationale for the choice.
	  ◦ Steady intracranial implant growth is not established prior to the initiation of treatment. This should be done by monitoring the BLI over at least two weeks following implantation and a threshold, like >5-fold increase in BLI signal, should be achieved prior to starting treatment.
	• While I appreciate the efforts to address sex as a biological variable, and the molecular heterogeneity of glioblastoma subtypes, the two male and two female specimens are unlikely to provide any insight into these important variables. This should be acknowledged and discussed.
	• The cellular fates of implanted progenitor cells must be evaluated. The expression of MHC should be measured along with the markers of stem/progenitor/differentiated cell markers.
	• The pitfall section doesn't include the true pitfalls of this project.

GWG Votes	**Is the proposal feasible?**
Yes: 8	• The team would benefit from inclusion of a neuro-oncologist and a developmental neuroscientist. • The potential pitfalls with respect to stem cell biology and oncolytic virus mediated killing are well presented. However, the PI has not discussed alternatives for the proposed transplantation studies.
No: 6	• This is a strong team. • The team has impressive results on previous CIRM rewards.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	• The product is anticipated to have equal efficacy in a diverse population. The design to produce an “off-the-shelf” cellular product would improve access to medically underserved areas. • The proposed work will develop anticancer therapy for glioblastoma irrespective of the tumor’s genetic background with a broad application to patients of any race, ethnicity, gender, and age. • The approach is likely to work (if it works) independent of racial background.
No: 1	*none*

Application #	DISC2-13533
Title (as written by the applicant)	Gene therapy vector correcting endoplasmic reticulum stress and GABA uptake defect in myoclonic atonic epilepsy
Research Objective (as written by the applicant)	We will develop a form of gene therapy based on silence-and-replace vectors that silence the mutant SLC6A1 gene but reconstitute GABA transport by expressing a synthetic gene that resists silencing.
Impact (as written by the applicant)	Our work could lead to a treatment for children with mutations in the SLC6A1 gene which cause epilepsy, intellectual disability, motor deficits, attention deficits, hyperactivity, and autism.
Major Proposed Activities (as written by the applicant)	• Use cellular models to develop silence-and-replace expression cassettes that suppress endogenous SLC6A1 expression but rescue GABA transport by expressing a synthetic gene that resists silencing. • Assess the contribution of endoplasmic reticulum (ER) retention of GAT-1 to seizures and behavioral phenotypes in SLC6A1 knockout mice (with no ER stress) or knockin mice (with ER stress). • Demonstrate efficacy of silence-and-replace vectors in SLC6A1 S295L knockin mice by assessing seizures (EEG) and relevant behaviors known to be affected by disease. • Combine data from Activities 1 and 3 to identify a clinical lead and set up proof of concept / safety cohorts in mice; define target dose for scale-up and for pivotal toxicology.
Statement of Benefit to California (as written by the applicant)	We propose a gene therapy approach to correct mutations in the SLC6A1 gene, a common cause of autism and myoclonic atonic epilepsy with poor prognosis. Seizures exacerbate developmental delay, and even a moderate relief of symptoms would have a huge impact on the everyday care of a child with this disease. The current treatments are not affordable to many patients especially those from under-served communities. If successful, our strategy could relieve symptoms with a single treatment.
Funds Requested	$1,283,566
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 65

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

Mean	66
Median	65
Standard Deviation	5
Highest	80
Lowest	60
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 11	• Myoclonic atonic epilepsy (MAE) is a significant seizure disorder due to lack of functional GAT-1 encoded by SLC6A1 transporter. This potential treatment could provide a treatment for MAE, if successful. • A mutation in the SLC6A1 gene is the causative mutation in Myoclonic atonic epilepsy (MAE), for which there is no cure and effective treatment. • A treatment for endoplasmic reticulum stress does exist, but this is high cost and not a direct treatment for GAT-1 deficiency. • A combined gene silencing and gene replacement approach to achieve higher saturation could address a critical bottleneck and shortcomings of other approaches • The applicant is aware that following this work, clinical trials of a candidate silence and replace vector will be needed. They have already considered enrollment criteria for such a next step. • If successful, a clinical trial could start relatively quickly..
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 8	• The rationale is sound and the approach is clever. A similar approach was used to treat oculopharyngeal muscular dystrophy, and has resulted in impressive suppression and gene replacement. • The idea of using a silence and replace approach is attractive, as dominant negative protein encoding mRNA might be destroyed with this approach, then replaced with a silencing resistant transgene. • Since some mutations in SLC6A1 lead to GAT-1 retention in the endoplasmic reticulum, this is likely caused by dominant negative effects. Hence, simple gene replacement therapies may not work, and the silence and replace approach is attractive. • There are many genes (perhaps at least 10 or 20 or more) that have been implicated by genome-wide association studies in MAE and also autism disorders. There is some risk that even if SLC6A1 function is restored, this may not have a large impact due to the many quantitative trait loci that may be involved in this disease. • There is not much preliminary data available. This is mostly an idea at present. The figures in the grant are mostly related to background information on MAE and the existing mouse GAT-1 deficient models. • The concern of the project being based on testing constructs that have not yet been developed remains a concern. No new data or candidates have been identified.
No: 4	• Would like to see more preliminary data.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 7	• The plan is overall good. • Because the project is in an early stage, without a vector and preliminary data that would support the interesting concept, the advancement to the clinic is difficult to evaluate.
No: 5	• If the research plan goes as planned, a candidate silence-replace vector may be available. • The research plan is logical. • This project is at its beginning, in planning stages only. However, it should be possible to design and validate silence-replace constructs directed at SLC6A1 in the course of this grant. • Would like to see more explicit, concrete, and responsive revisions in response to reviewers concerns.

GWG Votes	Is the proposal feasible?
Yes: 6	• The initial concern of the group being able to produce the proposed vectors within the proposed timeline have been mitigated by a more realistic timeline and a clear description of the groups expertise. • The investigator has decades of neurobiology research. A collaborator has experience in gene therapies. • It may be possible to get a vector ready for translation in a two year period, but this will only be if everything goes to plan. • The proposal relies on success of Aim 1 for which no data are provided. The tools are still not available to conduct the other aims. • The project is feasible once a vector is in hand.
No: 6	• The PI provides preliminary data supporting their expertise to assess the mouse model. However, as outlined in the first review, there is no preliminary data supporting the feasibility of the proposed project, only letters of support. • Unfortunately, the applicant was not responsive to previous reviews. As of now, this is just a good idea. • The milestones are logical but the project is overambitious for the proposed timeline.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 12	• The PI is aware that advanced technologies and state of the art medical approaches as not well accessed by underserved communities, and pledges to be cognizant of this issue in recruitment and analysis of patients and their associated medical data. • Epilepsies are prevalent in underserved communities, and there is no reason why this approach should not become available to them. • The cost of such a therapy and affordability are unclear.
No: 0	*none*

Application #	DISC2-13398
Title (as written by the applicant)	Bioinspired noncoding RNA chemical entity for Duchenne muscular dystrophy
Research Objective (as written by the applicant)	Modified synthetic noncoding RNA molecule
Impact (as written by the applicant)	Duchenne muscular dystrophy
Major Proposed Activities (as written by the applicant)	• Delivery route selection. • Develop and test preliminary potency assays based on mechanistic insights. • Demonstrate injury-modifying bioactivity of TY4 in muscle stem cells. • Optimize formulation and dosing of TY4, assessing biodistribution. • Explore the safety profile of TY4. • Prepare a Target Product Profile and a briefing document for an INTERACT meeting with CBER.
Statement of Benefit to California (as written by the applicant)	The target indication is Duchenne muscular dystrophy (DMD), a prematurely fatal disease refractory to medical intervention. DMD is prevalent in California and disproportionately afflicts disadvantaged populations, many of whom are of low socioeconomic status. In addition to high healthcare costs, non-medical expenses are in excess of $28k annually. Because the therapeutic candidate can be taken at home and is universally applicable, the societal benefits of success are expected to be profound.
Funds Requested	$1,397,412
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 60

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

Mean	59
Median	60
Standard Deviation	6
Highest	70
Lowest	50
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 9	• This proposal focuses on the evaluation of the therapeutic potential of the noncoding RNA entity identified in the extracellular vesicle cargo from human allogeneic cardiosphere-derived cells for the treatment of DMD. There is potential for impact since this noncoding RNA may be the component responsible for the biological activity observed in early clinical trials for DMD (therapeutic benefit). • The extracellular vesicle product seems to confer benefits in myocardial infarction and hypertrophy cardiac models. The PIs have now made a more stable, shorter therapeutic candidate TY4 based on this prior product. • The PI proposes to use a chemically-enhanced compound to treat Duchenne muscular dystrophy regardless of any mutation that causes it. • The concept of this approach, if supported by strong data, could result in a candidate that could impact pathology in Duchenne muscular dystrophy. • Yes, the proposed therapeutic candidate is likely to address the unmet need for DMD given its convincing preliminary data.
No: 5	*none*
GWG Votes	**Is the rationale sound?**
Yes: 6	• Currently, only a limited number of therapies targeting a small subset of DMD patients are available. The proposed therapeutic candidate has the potential to help a wide range of DMD patients.
No: 8	• The applicants assert that the mode of action of TY4 leads to an anti-fibrotic effect in skeletal muscles and heart, improves cardiac and muscle function, and enhances skeletal muscle regeneration. • Since the cytokine has been shown to improve the phenotype of the mdx model of Duchenne muscular dystrophy, the ability of prior product and the modified version TY4 to increase cytokine levels and the prior product's ability to increase acetylation in monocytes supports the scientific rationale of TY4 as a therapeutic for DMD. • Data from heart failure with preserved ejection fraction (HFpEF) also shows reductions of an inhibitor, which may be upregulated in dystrophic heart and skeletal muscle, although therapeutic effects of reductions have not been previously investigated. • The lack of preliminary data on the fibrotic diaphragm muscle, the measurement of cardiac function after only 8 weeks of treatment in mdx mice at an age when cardiac dysfunction is not present at baseline, and the entirely incorrect interpretation of muscle regeneration data do not support the premise. • No ages are given for the "aged" mdx 8 week treatment, however proposed studies will take place using an 8-week treatment in 12-14 month-old mdx mice. Since there are no reductions in EF or particularly quantifiable cardiac fibrosis in even mdx females at this point as reported by dozens of other groups over decades, the proposed cardiac studies will be uninformative. • The most relevant data for this proposal contained in Figure 4 is largely uninterpretable. No units are provided for the change in distance in the exercise capacity graph. Although statistically significant, it is not clear if the data is biologically significant since this could be millimeters or centimeters compared with a more biologically significant improvement by meters. It is also unclear whether this was a fatigue test (run until fatigued) or the distance run during a set time-period. • The data presented in Figure 5 is unclear. This data suggests that TY4 treatment reduced fibrosis that was already present in dystrophic heart and skeletal muscles, since this was only an 8 week treatment in "aged" mice. Some fibrosis would have been present before the treatment, so difficult to understand how it resolves. • Since mdx mice do not show reduced ejection fraction (EF) except in over 21 month-old females in this male X-linked disease, a change in ejection fraction without any further details is difficult to interpret. Heart rates must be maintained high (over 400 bpm) and equivalent between groups to compare EF, and if the control mdx mice are showing a ~15% reduction in EF from baseline over an 8 week period, the stress of gavage treatment (assuming they were given vehicle) must be causing major stress.

	• Quantification of cardiac fibrosis in vehicle treated mdx seems quite high at ~15% of ventricular area compared to previous reports for other, even more severe dystrophic models. • Entire transverse sections of hearts really need to be shown from mice at the age treatment was started in the treated mice, and in the treated and vehicle control mice. If half of the fibrosis resolves in the heart, what happens to that tissue? Is the fibrosis contracting? Is it being filled with inflammatory cells or fat? Since cardiomyocytes do not regenerate, it is not turning back into cardiac muscle. • There is a lack of preliminary data on the diaphragm muscle. • There appears to be inaccurate data in Fig. 6. Pax7 positive satellite cells are under the basal lamina (laminin staining) and Pax7 is downregulated almost immediately after satellite cells differentiate and is not detectable at the myofiber stage. Central nuclei in myofibers in regenerating muscle do tend to have non-specific staining and a secondary only control is required to correctly control for Pax7 staining. • Overall sound, but unfortunately the applicant does not provide sufficient information in the figure legends or description of results for us to understand if findings are compelling or not. Regardless, some results are not convincing. I have no idea what is quantified in Fig. 6, but I am certain these are not satellite cells.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 3	• Only female mdx mice will be used because of the cardiac phenotype, so it is unclear if the FDA will accept this data for treatment of an X-linked disease that affects males. • Discussion of anticipated results in Activity 3 makes predictions of outcomes "based upon known anti-apoptotic effects", but necrosis, and not apoptosis, is the mechanism of cell death in dystrophic muscles and heart. Also, myoblasts do not die in dystrophic muscle, since dystrophin is not even expressed at the myoblast stage. • Safety studies are only proposed in mice and another species is needed for IND.
No: 11	• Insufficient preliminary data. • Some of proposed studies are sound, while some experiments are not really addressing the goal of the project. The applicant does not clearly convey what the potential mechanism of action is. The rationale for experiments addressing bone marrow macrophages is unclear. Proposed potency studies in vitro using the C2C12 cell line do not address in vivo potential and efficacy. • The proposed assays to evaluate the bioactivity of the compound in vitro and in vivo are relevant. However, a direct experimental comparison between the proposed therapy and currently used therapies has not been addressed.
GWG Votes	**Is the proposal feasible?**
Yes: 9	• Milestones are logical and reasonable. • The proposed team is adept at cardiac studies, and has clearly demonstrated the expertise to chemically improve the therapeutic candidates. • The project is feasible but unlikely to generate meaningful data. • Yes, but it could be achieved in a shorter timeline given the experience of the team and the proposed experiments. • The PI has extensive experience in preparing regulatory documents for translating the proposed candidate. • A major weakness is the lack of expertise with DMD models to be able to pick the appropriate model and outcome measures for the proposed studies as well as correctly interpret data.
No: 5	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 12	• Since Latinos are more likely to be diagnosed with DMD, related medical and non-medical expenses are very high, and Latinos make up over 50% of all poor Californians, a less expensive therapy compared to emerging genetic therapies, would serve this population. • DMD affects males regardless of race or ethnicity therefore this project adequately addresses the influence of race, ethnicity, sex and gender diversity.

	• The project plan itself does not incorporate diversity, although the potential therapy would be useful and deliverable to males affected by the X-linked DMD regardless of community. One concern is that all experiments will take place in female mice due to the increased cardiomyopathy in females without considering alternative models where males can be treated.
No: 2	*none*

Application #	DISC2-13519
Title (as written by the applicant)	Drug Discovery for Duchenne Muscular Dystrophy Using Patient-Derived Human iPSCs
Research Objective (as written by the applicant)	Use a collection of ethnically diverse Duchenne muscular dystrophy (DMD) patient-derived heart cells via induced pluripotent stem cells to test therapeutics and discover new safe and effective drugs.
Impact (as written by the applicant)	Discover a drug that helps DMD-associated heart dysfunction, which is the leading cause of death in the disease with an urgent unmet need. We will also help with preclinical studies of rare diseases.
Major Proposed Activities (as written by the applicant)	• Clinical evaluation of DMD patients in the study to obtain the most up-to-date clinical information • Generate patient-specific and disease-specific heart cells to model the heart in DMD • Determine the extent of dysfunction in the heart cells derived from diverse DMD patients • Determine whether a drug identified can be a safe and effective drug for preventing fibrosis in the DMD heart • Discover a new drug for preclinical testing by performing a drug screen on the DMD heart cells • Determine whether the new drug discovered is safe and effective and works in patients of different ethnicities
Statement of Benefit to California (as written by the applicant)	Duchenne muscular dystrophy is a genetic disorder affecting 1 in 3,500 male births and thus thousands are estimated to be affected in California. In DMD, cardiomyopathies are highly prevalent and the leading cause of death in the disease. By discovering a safe and effective drug for these heart problems, we can help meet an urgent need for DMD patients and establish a proof of concept in applying induced pluripotent stem cell technology for the discovery of drugs for rare orphan diseases.
Funds Requested	$1,215,000
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: --

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

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

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 7	*none*
No: 7	• The project strives to identify small molecule therapeutics for DMD to treat or prevent cardiomyopathies associated with this disease. This represents an unmet medical need since DMD treatments are largely ineffective and cardiomyopathy represents the leading cause of death associated with DMD. • It is possible that development of well-characterized ethnically diverse induced pluripotent stem cell cardiac cells from Duchenne muscular dystrophy (DMD) patients will eventually be useful. Together with in vivo testing in animal models, they could be used to identify a candidate that could impact DMD cardiomyopathy. • The translation plan is early stage and unfocused. The project proposes early stage iPSC model development from DMD patients, evaluation of a candidate to target cardiac fibrosis, and screening of new drugs that influence cardiomyocytes. Each of these activities has value but the breadth comes at the cost of moving a promising technology toward translation. • The applicant does not discuss the advantages of developing a potential palliative treatment for DMD. The underlying cause of DMD is lack of dystrophin, not fibrosis. Importantly, the application totally ignores the literature of ongoing clinical trials of anti-fibrotic drugs for DMD. In addition, there is no clear rationale for seeking specific anti-fibrotic drugs for the heart. Fibrosis is a hallmark of skeletal and cardiac muscles in DMD. Both should be targeted, not only the heart.
GWG Votes	**Is the rationale sound?**
Yes: 5	• The premise of using iPSC-derived cardiac cells to identify new and characterize DMD drugs is strong and well-established. • The concept of using iPSCs from diverse patient populations is an interesting way to account for patient-specific responses early in drug development. • Defining the variability in numerous induced pluripotent stem cell cardiomyocyte (iPSC-CM) outcomes across an ethnically diverse set of samples has strong rationale. This would useful for developing potential therapies for DMD cardiomyopathy that are useful for all patients, or to be able to screen for non-responders prior to treatment. • The rationale for using these cells to improve drugs is not strong. These types of drugs can and have been tested in many available types of cells. The clinical issue with the current efficacy of these drugs is a delivery issue and not an efficacy issue at the cellular level, or the unavailability of personalized reagents for testing these therapies. • The team demonstrates iPSC-CM phenotypes associated with DMD in patient-derived cells, including calcium handling, metabolism, and response to beta-adrenergic stress. • The use of the iPSC derived cells for testing novel anti-fibrotic therapies may have value, although only one drug will be tested, and its relevance in DMD cardiomyopathy is unknown. The activation of alpha-smooth muscle actin and Collagen I by conditioned media from DMD iPSC-CMs on primary cardiac fibroblasts strongly supports the rationale for this assay. • A candidate molecule (adenosine receptor inhibitor) has been identified that inhibits cardiac fibroblast activation. It isn't clear that this has been tested in their DMD cells, however. • It is interesting that the DMD cardiomyocytes upregulate activation markers in the fibroblasts, but the relevance of this to fibrotic disease is speculative at this point. • The notion of using cell-level responses to predict complex tissue and organ physiology in cardiac fibrosis seems simplistic. Evaluation of these predictions in animal models would strength the approach.

No: 9	• All proposed work is in vitro. One goal is to test the effect of 3 doses of the drug to inhibit the secretion of fibrotic substances by the conditioned media of iPSC-CMs, thus potentially preventing myofibroblast activation. These in vitro studies do not recapitulate what will happen in the in vivo environment. • The applicant proposed screening for molecules that rescue cell survival. Hundreds of small molecules have been identified to enhance survival in vitro. How many were translated to the clinic?
GWG Votes	**Is the proposal well planned and designed?**
Yes: 3	*none*
No: 11	• Major strengths include the measurement capabilities for iPSC-CMs and the wide array of outcome measures proposed to characterize the cells in Aim 1. • A major strength is the generation of cardiac fibroblasts and the use of conditioned media to induce a response for drug testing. • The screen in iPSC-CMs in Aim 2 is well-designed to identify lead compounds that reduce toxicity. • DMD model development is well-considered. Phenotypic assessment is strong and comprehensive. • The activities are broad and diffuse, involving developing new models, investigation of an existing candidate to target cardiac fibrosis, and preliminary screening for drugs that reduce stress-associated death of cardiomyocytes. • The somewhat disconnected multi-targeted approach rather than a focus on one cell type and mechanism is a weakness. Although both cardiac fibroblast and cardiomyocyte studies are highly relevant, the diffuse nature of the grant may lead to less overall productivity towards translation. • Successful completion of the project would result in very early stage evaluation in iPSC models. The project does not address safety issues or proof-of-concept efficacy in more physiologic models. • Developing iPSC-DMD models from patients from diverse backgrounds where long-term tracking of disease progression is possible has potential long-term benefits in personalized drug discovery and development. • The applicant has access to a bank of ~30 DMD iPSC lines. While there is value in adding diversity, it isn't clear why this specific project needs the additional lines generated in Aim 1. • A major to moderate weakness is the absence of cardiac therapies currently used in DMD, including ACE inhibitors, mineralocorticoid receptor antagonists (MRAs) and sGLT2 inhibitors. In particular, since the major screening assay is based on viability, MRAs should be used as a control since these drugs have been shown to stabilize dystrophic cardiomyocytes in vivo, and skeletal muscle myocytes in vivo and in vitro, and have demonstrated efficacy above ACE inhibitors in DMD clinical trials. • Only one drug will be tested and the potential relevance of the receptor to dystrophic cardiomyopathy is entirely unknown. • Antifibrotic effects of the receptor antagonist are cursory, solely involving expression of two markers in cardiac fibroblasts. While these are established activation markers, the relevance to the pathophysiology of cardiac fibrosis in DMD is not clear. • The validation plan for the candidates is very cursory. It isn't clear that this is the mechanism of cardiotoxicity in DMD and the path to evaluating efficacy and safety of the screen hits is vague. • Off-target effects and safety of the lead compound is not considered. The receptor is widely expressed in many tissues. • There is no discussion on next steps in the case a potential compound is identified. It is stated that safety and efficacy will be tested, but the proposed experiments do not really address these important parameters. • These in vitro studies may be a good starting point but not very meaningful. • A major weakness is no discussion of future in vivo assays in DMD mouse models (which models will be chosen, how assays could be carried out) for any potential therapeutic candidates identified in this study. • After secondary screening and validation of hits, they propose a pre-IND (direct from a screen to the FDA?).

GWG Votes	Is the proposal feasible?
Yes: 8	• Milestones and timeline are achievable. • The milestones are reasonable to achieve in the project time window. • The milestones are largely qualitative. Quantitative success criteria would strengthen the proposal. • The proposed team is qualified and staffed appropriately for the proposed experiments. Additional muscular dystrophy animal model experts will need to be consulted/added in the future to take any candidates to in vivo testing. • Good expertise within the team. • The team is outstanding. The institution and collaborators have the expertise to perform this project. The team contains pioneers in iPSC-based disease modeling and personalized medicine.
No: 6	• Some milestones are feasible, but project is really non-ambitious. The first milestones are really not meaningful in terms of addressing the main goals of the project. The "real experiments" start only at Year 2 (milestones 4, 5, and 6).
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	• Ethnic diversity is a major goal of the study and is well-addressed. • The project does an excellent job in considering race and ethnic diversity through patient-specific iPSC lines. It isn't clear that the 10 lines generated will have the power to identify differences in drug response by community, but the consideration of diversity is strong.
No: 1	*none*

Application #	DISC2-13491
Title (as written by the applicant)	An Engineered Exosome Nanocarrier System for Delivering Gene Therapy to Lung Cancer Stem Cells
Research Objective (as written by the applicant)	We use CRISPR Cas9 to knockout the oncogene KRAS in 30% of lung cancers, to induce cancer stem-cells death. Delivery of CRISPR is done through exosomes, nanovesicles involved in cell communication.
Impact (as written by the applicant)	It can change the outcomes in Black American men with highest death rates and shortest survival of any group, as well as veterans with higher risk and survival rates much lower than overall population
Major Proposed Activities (as written by the applicant)	• We will optimize each process of lung stem cell-derived exosome preparation from isolation to CRISPR-Cas9 loading, to increase the yield of high-purity and quality for next experiments in vivo. • We will prepare different formulations of exosomes carrying CRISPR-Cas9 and compare their activity in vitro against KRAS mutated cancer cell lines to decide the one we keep for in vivo mouse models. • We will determine the recommended dose of the exosomes for future experiments in mouse models. For that purpose we will test different dose levels in healthy mice, monitor them and check tolerability. • To confirm that exosomes obtained from lung progenitor stem-cells concentrate in lung cancer tissue ignoring normal organs, we will label them with a luminescent enzyme before injecting them in mice. • We will compare safety and efficacy of exosomes carrying CRISPR Cas9 to current human treatments, injected in mice with lung cancer. The mice will be monitored and their survival will be measured. • At the end of this project, to simplify the treatment and have only one to treat patients with different mutations, we will modify CRISPR Cas 9 and make it able to target different KRAS mutations.
Statement of Benefit to California (as written by the applicant)	Lung cancer is still the leading cause of cancer-related deaths, despite decades of research and investment and California ranks 3rd among all states. It affects people of all races and ethnicities, with a heavier burden on some vulnerable populations, such as Black Americans and Military Veterans, who are more likely to develop it and face lower survival rates. Our approach is expected to provide an effective treatment with a favorable safety profile and help patients from these vulnerable populations.
Funds Requested	$1,201,524
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: --

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

Mean	--
Median	--
Standard Deviation	--
Highest	--
Lowest	--
Count	15

(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 6	• If successful, the proposal could lead to development of new therapies. • No concerns on the significance in targeting KRAS-altered lung cancer.
No: 8	• The proposed research plan is too premature for consideration of potential impact. There is no proof-of-concept that exosomes will have tropism for lung cancer, that the investigators can load exosomes with Cas9, or that editing of KRAS mutations is specific and/or leads to death of tumor cells.
GWG Votes	**Is the rationale sound?**
Yes: 3	*none*
No: 11	• There is limited preliminary data, especially around targeting lung and tumor cells specifically. • Very little to no preliminary data included to justify the proposal. The panel would need to see in vivo data showing exosome trafficking to tumors, as this is unclear. • Design of sgRNAs to target each mutation does not seem feasible. The investigators have not disclosed sequences or demonstrated selective knockout based on the mutation.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 2	*none*
No: 12	• This reviewer struggled to follow the chain of experiments as outlined. • It is unclear why these exosomes would traffic to tumor over normal lung. • Experimental plans are very detailed, similar to a protocol (no need for catalog number or source company). Plans are typically less detailed. Strong rationales for these experiments with definitive positive and negative controls are needed.
GWG Votes	**Is the proposal feasible?**
Yes: 3	*none*
No: 11	• With limited preliminary data, the feasibility of this project is unclear. • Preliminary data demonstrates no ability to edit cells with CRISPR alone or in exosomes. No evidence that Cas9+sgRNA can be loaded into exosomes by the investigator. The only data provided are transfection efficiency and cell growth post gene editing without evidence of the editing. • No demonstration that exosomes from the cell line have tropism for lung cancer cells. This could have been demonstrated with GFP mRNA or with CRISPR/Cas9 + positive control sgRNA. • It is unclear if enough exosomes can be generated feasibly for translation.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 12	• The project could serve the needs of underserved communities

No: 2	• No evidence that this technology would serve the underserved. Exosomes require stringent purification and manipulation and the cost of manufacturing should be considered in the context of treatment affordability.

Application #	DISC2-13506
Title (as written by the applicant)	Bi-functional immune therapy for lung cancer
Research Objective (as written by the applicant)	The objective is to develop bifunctional immune therapy for lung cancer targeting cancer stem cells and cancer stroma progenitors.
Impact (as written by the applicant)	Very few therapies targeting cancer stem cells are approved and none exists targeting the tumor stroma. We here propose to develop a single drug for lung cancer that is able to eliminate both.
Major Proposed Activities (as written by the applicant)	• Activity 1: Development of bifunctional biologic candidates • Activity 2: Evaluation of therapeutic efficacy in model systems • Activity 3: Determination of mechanism of action of biologic candidate
Statement of Benefit to California (as written by the applicant)	With an average annual death rate of 26.7 per 100,000 Californians lung cancer is responsible for most cancer deaths in the state. This proposal aims to overcome a critical bottleneck in current cancer therapy approaches by engaging a two-pronged attack on different cancer properties. If successful, Californians suffering from lung cancer will benefit from higher life expectancy and quality of life, in turn positively impacting California's society and economy.
Funds Requested	$1,287,936
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

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

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

KEY QUESTIONS AND COMMENTS

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

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

Yes: 3	• If successful, the project could lead to development of a new innate checkpoint, but it is unclear why this would be superior to other targets. • It is unclear if cancer stem cells or all cancer cells express the target.
No: 11	• There is a clear unmet clinical need for better treatments for lung cancer and lung fibrosis. • The proposed work will address the potential of blocking the target on lung cancer stem cells (CSCs) and pathogenic fibroblasts as a way to inhibit a putative 'do not eat me' signal. • The PI provides supporting preliminary evidence to show that in a mouse model, loss of the target expression can enhance efferocytosis by macrophages. • This project aims to treat lung cancer. This project is focused on cancer research and has little impact on stem cell research or technology. • The applicant did not present sufficient evidence for translation of their technology. • Superiority of the approach not addressed. • Unfortunately, the proposed technology will not be properly tested. This is major fatal flaw of the proposed work.
GWG Votes	**Is the rationale sound?**
Yes: 3	• I don't believe antibody alone is sufficient to cure lung cancer. The protein could be a target for treating lung cancer. • More data is needed for in vivo testing of the antibody, especially off-target effects. • This is cancer research and may be more appropriate for submitting to NIH.
No: 11	• The main rationale for the work is based on intriguing and provocative preliminary evidence showing that target deficient cells are more actively taken up by macrophages. • The preliminary data support the notion that blocking the target could lead to increase clearance of cancer stem cells and pathogenic lung fibroblasts. But the model to be used to test this is flawed. • Unclear how human mAb development in a mouse model which will have murine macrophages and fibroblasts with human tumors will allow for delineation of effect. • The wrong model is proposed. • No humanized model.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 2	• The applicant did not provide sufficient alternative approaches.
No: 12	• The proposed work is outlined as three main aims. The aims will develop the therapeutic candidate in form of a blocking antibody using immunization of mice and monoclonal antibody generation, which will be contracted out. • Aim 2 will validate and evaluate biologic candidates from Aim 1 for therapeutic efficacy in a mouse model of lung cancer, in a human lung cancer xenograft model, and in a mouse model of lung fibrosis. Unfortunately, the use of these mouse models will not be able to test the function of an anti-human antibody, as the mouse models will express mouse antibody. This is a major fatal flaw. • The human xenograft is slightly better, but this suffers from the graft being rejected by the mouse immune system. • Given the flaws associated with Aim 2, it is difficult to fully appreciate the proposed work in Aim 3. • Experiments would be preferable in completely humanized systems. • Off-target effects are not addressed.
GWG Votes	**Is the proposal feasible?**
Yes: 5	• The proposal should be feasible, but ambitious.
No: 9	• It may take more than two years to finish this project. • The proposed work is not well-structured and suffers from a fatal flaw in the study design. • The PI provides a set of pitfalls and alternative approaches but fails to appreciate that antibodies made in mice against human antibody will not react to mouse antibody. • No, the proposed aims are not well-designed and not feasible.

GWG Votes	Does the project serve the needs of underserved communities?
Yes: 13	• Yes, the PI points out and addresses these factors in the proposal. • The project serves the needs of underserved communities.
No: 1	*none*