APP #	TITLE	BUDGET REQ	FUND	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Product Type	Approach
DISCOVERY APPLICATIONS												
DISC2-12169	Human-induced pluripotent stem cell-derived glial enriched progenitors to treat white matter stroke and vascular dementia.	$250,000	**Y**	**95**	94	2	90	98	14	0	Cell therapy	Development of an allogeneic iPSC-derived glial progenitor cell therapy candidate for stroke/vascular dementia
DISC2-12111	Hematopoietic Stem Cell Gene Therapy for X-linked Agammaglobulinemia	$250,000	**Y**	**90**	91	2	90	95	15	0	Cell and gene therapy	Development of an autologous gene-corrected HSC candidate tot reat X-linked agammaglobulinemia
DISC2-12170	Development of COVID-19 Antiviral Therapy Using Human iPSC-Derived Lung Organoids	$250,000	**Y**	**90**	91	3	85	95	14	0	Small molecule anti-viral	Use of an iPSC-derived lung organoid model to identify drug candidates for SARS-CoV2 infection
DISC2-12158	Development of a SYF2 antisense oligonucleotide (ASO) treatment for ALS	$249,997	**Y**	**90**	91	3	88	98	13	0	Biologic	Use of patient iPSC-derived motor neurons to identify antisense oligonucleotide candidates to treat ALS
DISC2-12124	Dual angiogenic and immunomodulating nanotechnology for subcutaneous stem cell derived islet transplantation for the treatment of diabetes	$250,000	**Y**	**88**	89	4	85	95	15	0	Cell therapy	Development of iPSC-derived islet-like organoid candidate for subcutaneous delivery and treatment of diabetes
DISC2-12105	Human iPSC-derived chimeric antigen receptor-expressing macrophages for cancer treatment	$250,000	**Y**	**87**	87	2	80	90	14	1	Cell and gene therapy	Development of an iPSC-derived CAR macrophage therapy candidate to target cancer cells including ovarian cancer
DISC2-12164	Optimization of a human interneuron cell therapy for traumatic brain injury	$250,000	**Y**	**85**	85	2	80	87	12	2	Cell therapy	Development of an iPSC-derived inhibitory neuron candidate to restore neurologic function after traumatic brain injury
DISC2-12172	Combating COVID-19 using human PSC-derived NK cells	$249,998	**Y**	**85**	85	4	80	90	8	7	Cell and gene therapy	Development of a gene-edited, PSC-derived NK cell candidate to target SARS-Cov2 infected cells
DISC2-12126	The First Orally Delivered Cell Therapy for the Treatment of Inflammatory Bowel Disease	$249,000	**Y**	**85**	83	5	70	90	8	6	Cell therapy	Development of an orally administered, encapsulated MSC therapy candidate for IBD
DISC2-12130	Transplantation of Pluripotent Stem Cell Derived Microglia for the Treatment of Adult-onset Leukoencephalopathy (HDLS/ALSP)	$249,968	**Y**	**85**	82	5	75	90	7	6	Cell therapy	Development of a PSC-derived microglial cell candidate for replacement of damaged/diseased microglia
DISC2-12098	Glial-restricted neural progenitor cells as a treatment for Rett syndrome	$250,000	**N**	**80**	80	11	50	95	7	8		
DISC2-12123	Rejuvenation of intervertebral disc with iPSC-derived notochordal cells to treat low back pain in wild type and diabetic rat model	$250,000	**N**	**80**	77	7	60	85	3	12		
DISC2-12155	iPSC-based secretomes for treatment of pelvic organ prolapse	$250,000	**N**	**80**	76	8	60	85	3	12		
DISC2-12145	Engineering MSC formulation to improve survival and efficacy in vivo	$249,998	**N**	**75**	75	8	60	87	2	13		
DISC2-12121	Targeting Mesothelioma Using HSC-Engineered Off-The-Shelf CAR-iNKT Cells	$250,000	**N**	**70**	71	1	70	75	0	14		
DISC2-12171	Spheroids of neural crest stem cells for neuromuscular regeneration	$250,000	**N**	**70**	71	4	65	80	0	13		
DISC2-12157	Molecular manual for human hematopoietic stem cell development	$250,000	**N**	**69**	67	6	50	75	0	14		
DISC2-12135	Prevention of Neuromuscular Junction Loss in Amyotrophic Lateral Sclerosis	$250,000	**N**	**65**	68	9	60	85	1	13		
DISC2-12107	Ameliorating drug-resistant human pancreatic cancer stem cells.	$249,389	**N**	**62**	61	5	50	65	0	14		

APP #	TITLE	BUDGET REQ	FUND	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Product Type	Approach
DISCOVERY APPLICATIONS												
DISC2-12106	A Controlled Release Biomaterial for Improved Survival, Innervation, and Functionality of DA Neuron Cell Replacement Therapy for Parkinson's Disease	$248,840	**N**	**60**	62	4	55	70	0	14		
DISC2-12141	Assessment of Novel Depots of Adipose-Derived Stem Cells for Chronic Rotator Cuff Injury	$250,000	**N**	**60**	62	6	50	75	0	15		
DISC2-12144	Differentiation of Vd1 gd T Cell-derived Pluripotent Cells for Use in Solid Tumor Cell Therapy	$250,000	**N**	**60**	59	3	50	60	0	15		
DISC2-12184	Engineered injectable pre-vascularized implant for neural stem cell transplantation after stroke	$250,000	**N**	**60**	59	13	30	75	0	14		
DISC2-12102	Treatment of Abdominal Aortic Aneurysm Using Scaffold-Based Delivery of iPSC-derived Smooth Muscle Progenitor Cells	$250,000	**N**	**58**	58	6	50	70	0	14		
DISC2-12113	Skeletal stem cells for the treatment of Osteoporosis	$240,628	**N**	**55**	54	4	50	60	0	15		
DISC2-12103	Small molecule neurotherapy for genetic Complex 1 disorders in children	$249,863	**N**	**-**	-	-	-	-	0	14		
DISC2-12134	Vascularized Cancers for Angiogenesis and Metastasis	$250,000	**N**	**-**	-	-	-	-	0	13		
DISC2-12151	Hematopoietic Stem Cell Extracellular Vesicle-Mediated RNAi to Target Oncogenes	$249,998	**N**	**-**	-	-	-	-	0	13		
DISC2-12096	Identifying Exposure to SARS-CoV-2 using Novel Peptide Antigens to Elicit CD8+ T Cells	$250,000	**N**	**-**	-	-	-	-	0	15		
DISC2-12156	Superiority of BACS automated isolation of CD34+ cells in sterile "functionally closed" process cartridge over manual, "open system" Ficoll/MACS.	$180,200	**N**	**-**	-	-	-	-	0	15		
DISC2-12166	Activation of Endogenous Stem Cell Repair After Myocardial Infarction	$249,914	**N**	**-**	-	-	-	-	0	14		

Application #	DISC2-12169
Title (as written by the applicant)	Human-induced pluripotent stem cell-derived glial enriched progenitors to treat white matter stroke and vascular dementia.
Research Objective (as written by the applicant)	This grant proposes development of a stem cell based therapy that is derived from human induced pluripotent stem cells. These cells are in the form of a brain support cell, an astrocyte.
Impact (as written by the applicant)	The cell candidate will treat vascular dementia, the second leading cause of dementia, and stroke by overcoming a bottleneck in the ability to make large quantities of the cells for clinical use.
Major Proposed Activities (as written by the applicant)	• In vivo tumorigenic studies. • Development and optimization of potency assays • Qualification and stability of cell delivery system.
Statement of Benefit to California (as written by the applicant)	This research will develop a therapy for a disease with no treatment, vascular dementia, that is common and devastating in its consequences. The intellectual property for this therapy is held by a State of California public university (UCLA) and commercialization will directly benefit the State of California.
Funds Requested	$250,000
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 95

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

Mean	94
Median	95
Standard Deviation	2
Highest	98
Lowest	90
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 13	• The proposal seeks to develop an allogeneic human iPSC derived Glial Enriched Progenitor (GEP) cell therapy product to treat white matter stroke and vascular dementia. This is an unmet medical need, and not many other groups are working on this problem. • White matter stroke, is a widespread problem with no therapy that stabilizes the disease or prevents further progression. The impact could be significant. • The cellular targets in white matter stroke are primarily astrocytes and oligodendrocytes making it an excellent candidate for cell replacement therapies. • Critical data has been already collected and the proposed extension of the work that includes completing product formulation, assay development and in vivo testing should result in pre-IND meeting with the FDA, and accelerated progress towards a clinical trial.

	• The applicant team has successfully developed per clinical protocols for the graft cell population (safety, identity, purity and stability qualification assays). • Treatments for stroke are sorely needed.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 13	• The rationale is sound as the target cell population is a match. • Yes, transplantation of pro-repair astrocytes has been shown promise in a number of approaches. • Applicant has established efficacy of hiPSC-GEPs transplantation and determined the appropriate therapeutic time window, location and dose of hiPS-GEPs that is needed to see functional benefits. • Key factors that play a mechanistic role in the hiPSC-GEPs associated repair process have been determined although their contribution to repair is not clear. • Great application with sound rationale.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 13	• Yes, the critical steps needed for the development of the product are clearly described. This includes production under GLP/GMP conditions, among other things. • Exemplary application. • GLP toxicology and GMP master cell bank production are a critical part for therapeutic development. • The analyses of tumorigenic potential of hiPSC-GEPs in vitro and in vivo is standard in the field. • Milestone 2 and 3 are necessary steps towards a clinical product. • Variability tolerance for the RNA sequencing footprint is not discussed and gene expression profiles of frozen thawed cells are not re-tested. • Freeze thawing might alter cell function and efficacy. At least one in vivo functional recovery experiment should be performed with frozen-thawed cells injected in the clinically relevant manner. • No concerns noted.
No: 0	*none*
GWG Votes	Is the proposal feasible?
Yes: 13	• Yes, the project milestones are well articulated and action orientated. • Proof of concept provided. • Milestone 3 should perhaps have priority. • Milestones are well specified.
No: 0	*none*

Application #	DISC2-12111
Title (as written by the applicant)	Hematopoietic Stem Cell Gene Therapy for X-linked Agammaglobulinemia
Research Objective (as written by the applicant)	The objectives of this study are to advance a stem cell gene therapy for the immunodeficiency XLA, defining the final therapeutic candidate and showing therapeutic activity in a relevant mouse model.
Impact (as written by the applicant)	XLA can be treated with chronic immunoglobulin replacement, but may be sub-optimal due to infections and inflammatory complications. Stem cell gene therapy may provide a curative one time treatment.
Major Proposed Activities (as written by the applicant)	• 1. Assess BTK lineage expression and humoral immune reconstitution in BTK/TEK double knock-out mouse model of XLA by BTK gene editing and transplantation to demonstrate disease modifying activity. • 2. Compare different BTK transgene expression units for the lineages, levels and lymphocyte function they produce to define optimal candidate. • 3. Assess safety of BTK editing by secondary transplants of edited cells into congenic (CD45.1) recipients. • 4. Establish draft Target Product Profile. • 5. Develop measures of identity, activity and purity. • 6. Define therapeutic candidate, based on results of above studies
Statement of Benefit to California (as written by the applicant)	Regenerative medicine methods using genetically-corrected human stem cells will result in novel, effective therapies for blood cell diseases to improve the health of millions of Californians and tens of millions of people world-wide. Scientific findings and biomedical materials produced will be publicly available to non-profit and academic organizations in California, and any intellectual property developed by this Project will follow the guidelines of CIRM to benefit the State of California.
Funds Requested	$250,000
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 90

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

Mean	91
Median	90
Standard Deviation	2
Highest	95
Lowest	90
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	15
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• X-linked agammaglobulinemia (XLA) is a primary immune deficiency caused by a deficiency in the BTK gene. Allogeneic transplants are currently used to treat this disease.

	Although potentially curative, allogeneic transplants are potentially fraught with safety issues. The proposed approach of gene modified autologous HSCs has been used in other primary immune deficiencies and has a high probability of success. ● Current therapies are expensive, partially effective or/and high risk. ● Would also inform the field in general about gene editing approaches. ● This work will help identify a candidate to treat XLA and could open the door to additional rare disease treatments. ● Major strengths are: Excellent team with world-class expertise for both genetic manipulation of HSC and for stem cell transplantation in inherited diseases; having access to murine model of XLA. ● Only minor concern is to first validate stated assumptions regarding FDA regulatory requirements for potential pediatric patients (i.e., is demonstrated efficacy/safety in the murine model absolutely necessary, and if yes then are the proposed studies sufficient to accomplish those goals).
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 14	● Need for appropriately regulated BTK expression is well-established, thus need for the gene correction strategy is clear. ● The authors propose to use gene editing to enable targeted insertion of the BTK gene. The grant applicants have put together a nice set of preliminary data demonstrating that they can insert the BTK cassette in human primary CD34+ cells and in cell lines. ● Due to the high FDA approval bar of bringing a therapy to a pediatric patient group, pre-testing in a murine model seems reasonable. ● Requirement for a murine model by the FDA is an assumption. The need should be confirmed and clarified. ● No major concerns.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 14	● Entire application and proposed set of studies was very clearly presented. ● Yes, the project is well planned and has a high probability of producing a viable clinical candidate. ● Well constructed with only minor issues. ● One suggestion is to have a pre-IND or INTERACT meeting with FDA and amend milestones to support work that truly helps move this into the clinic. ● AAV vector integration should be monitored.
No: 0	*none*
GWG Votes	Is the proposal feasible?
Yes: 14	● Proposed experiments are designed very well, the team has all the required expertise to complete the studies within the specified time. ● Yes, there is a high probability of success. This is a world-class team that has pioneered many aspects of HSC gene therapy. They are very well positioned to be successful. ● Very strong team with an appropriate timeline. ● AAV integration might be challenging.
No: 0	*none*

Application #	DISC2-12170
Title (as written by the applicant)	Development of COVID-19 Antiviral Therapy Using Human iPSC-Derived Lung Organoids
Research Objective (as written by the applicant)	To develop a new therapy for COVID-19 using human iPSC-derived lung organoids that targets SARS-CoV-2 protease known as the virus' "Achilles Heel"
Impact (as written by the applicant)	Our work, if successful, will bring a class of new drugs directly targeting viral enzyme and open the door for future COVID therapies.
Major Proposed Activities (as written by the applicant)	• Complete synthesis and testing of new inhibitors • Optimize and validate the new compounds activities in lung cells and organoids • Rapidly expand the efficacy of SARS-CoV-2 inhibitors in a large panel of lung organoids from African-American, Latino, and Caucasian men and women. • ensure that any newly emerging therapy will be applicable to all patients regardless of gender and race.
Statement of Benefit to California (as written by the applicant)	The emergence of novel coronavirus SARS-CoV-2 and its associated disease, COVID-19, has presented an urgent global public health crisis. In California, more than 700,000 individuals have been infected leading ~13,000 deaths. Further, Californians are grappling with the economic impact due to job loss and business shutdowns. Finding a treatment for COVID-19 would have a huge impact on saving lives, preventing new infections, and helping people to return to normal activities of life.
Funds Requested	$250,000
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 90

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

Mean	91
Median	90
Standard Deviation	3
Highest	95
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. Following the panel's discussion and scoring of the application, the scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 13	• This is a great proposal. An elegant approach to develop alternative anti-viral therapies. • This proposal could be significant given the desperate need for COVID therapies although it may be comparatively more expensive than other therapies. It could also have broad applicability to other diseases due to the off the shelf nature. • Highly significant and timely.

	• Organoid model of a variety of populations. • Antiviral could be a major benefit.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 13	• Great pre-clinical models and very nice medicinal chemistry. • Given the potent antiviral capacity of NK cells and the strong preliminary data for this study the rationale is very strong. • Potential alternative to vaccines.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 11	• There are no significant concerns. • Overall yes, but the project still would have benefited from showing a real killing assay against SARS-CoV-2-infected cells. • All aspects are well developed. • Selection of compounds with which to go forward not well defined.
No: 2	• Few, if any potential pitfalls are outlined. This is a concern.
GWG Votes	Is the proposal feasible?
Yes: 13	• This is a great team, with outstanding expertise in the different fields required to complete the proposed studies. • I think the project is quite feasible within the timeline and that the investigators are capable of executing most of the assays. The proposed milestones seem reasonable and I think the team is very strong and the institutions should have all the facilities they need to complete the proposed studies. The budget seems mostly reasonable. • Good change of success. • Could have added a more detailed pitfall section.
No: 0	*none*

Application #	DISC2-12158
Title (as written by the applicant)	Development of a SYF2 antisense oligonucleotide (ASO) treatment for ALS
Research Objective (as written by the applicant)	We will develop an antisense oligonucleotide, or DNA therapy for diverse forms of amyotrophic lateral sclerosis (ALS).
Impact (as written by the applicant)	ALS is fatal and incurable, and if successful, we will develop a treatment that slows or stops ALS progression across a broad range of patients.
Major Proposed Activities (as written by the applicant)	• Selection of the lead drug by testing several candidates for efficacy and safety on ALS patient-derived nerve cells. • Confirmation that the lead drug is effective and stable in mice. • Confirmation that the lead drug is safe in mice.
Statement of Benefit to California (as written by the applicant)	ALS is a fatal, incurable disease and California has one of the highest number of ALS patients of any state. By testing our drug on stem cell-derived nerve cells from Californian ALS patients, we will increase the chances that it will be effective on the types of ALS patients found in California. If successful, our drug will substantially slow or stop ALS disease progression.
Funds Requested	$249,997
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 90

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

Mean	91
Median	90
Standard Deviation	3
Highest	98
Lowest	88
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 12	• Gene therapy cannot address the vast majority (85%) of cases of ALS that have an unknown genetic etiology. The proposal discussed a new therapeutic strategy using antisense oligonucleotide (ASO) that suppresses the expression of the RNA export factor SYF2 as a therapeutic approach for diverse forms of ALS. • The use of motor neurons derived from patients with a known genetic cause of ALS and motor neurons derived from sporadic ALS patients is a great strength of this project. • Includes sporadic cases. • Based on a common molecular target in many ALS cases.

	• Ideas about development of the proposed therapeutic are well-thought-out, and other antisense strategies have proceeded to clinical examination. • This is an appropriate high risk, high reward project to get a therapeutic for ALS.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 11	• The project is based on a very interesting observation that 97% of all ALS cases show TDP-43 mis-localization from the nucleus to the cytoplasm in nerve cells, and that disruption of normal TDP-43 function can cause neurodegeneration. • New approaches are based on development of strategies to suppress the RNA binding protein SYF2, with this target identified as a consequence of unbiased screening of drugs and other small molecules to find agents that support ALS motor neuron survival. • The preliminary data seems strong to motivate a groundbreaking approach. • Yes, there is a strong link between SYF and TDP43. • Knockdown of target is reasonable as haploinsufficiency of the target is non disease carrying.
No: 1	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 12	• Most critically, in my view, are data demonstrating that SYF2 suppression is able to rescue neurons in appropriate mouse models of TDP-43 dysfunction. These mice develop motor deficits, neurodegeneration and paralysis by about Day 24, and treatment provided useful benefits. • The use of motor neurons derived from patients with a known genetic cause of ALS and motor neurons derived from sporadic ALS patients is a great strength of this project. • No concerns about the plan. • Planning is adequate.
No: 0	*none*
GWG Votes	Is the proposal feasible?
Yes: 12	• Yes, as many key data sets are in place already. • The project is extremely well-planned and well thought out. • A great deal of thought has been given to considering pitfalls in advance and working to overcome them. • Yes - no concerns are noted.
No: 0	*none*

Application #	DISC2-12124
Title (as written by the applicant)	Dual angiogenic and immunomodulating nanotechnology for subcutaneous stem cell derived islet transplantation for the treatment of diabetes
Research Objective (as written by the applicant)	Functional human islet like organoids differentiated from human pluripotent stem cells.
Impact (as written by the applicant)	Providing the immediate cell therapeutic candidate for clinical trial of diabetic patients.
Major Proposed Activities (as written by the applicant)	• Fabrication and characterization of the injectable immunomodulating and pro-angiogenic material components: HA hydrogel, heparin nanoparticles and VEGF clusters. • Generation of human islet like organoids from pluripotent stem cells for subcutaneous transplantation • Subcutaneous HILOs transplantation in pre-vasculature site in NOD-SCID mice. • Subcutaneous PD-L1 expressing HILOs transplantation in pre-vasculature site in Hu-PBMC-NSG mice
Statement of Benefit to California (as written by the applicant)	The cell and technology products proposed by this diabetes therapeutic study will significantly improve future diabetes treatments in the State of California, particularly benefiting vulnerable populations, such as Hispanics, African-Americans, men, older populations, homeless individuals, and those of lower socioeconomic status. Additionally, this proposed research may create greater research employment opportunities in the South Bay, a region within Los Angeles County.
Funds Requested	$250,000
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 88

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

Mean	89
Median	88
Standard Deviation	4
Highest	95
Lowest	85
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	15
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• Generation of a transplantable substitute for human pancreatic islets remains a "grail" of regenerative medicine to address needs of individuals with Type 1 diabetes (T1D) that is

	not well controlled by insulin injection. In principle, such a product could offer a cure for T1D. ● There is no cure for diabetes, which affects nearly 3 million people in California. Donor islets are in short supply for transplantation, necessitating stem cell technology. Because of the autoimmune destruction of transplanted cells that produce insulin, it is essential to develop approaches that allow beta cells to function protected from immune attack. ● If the objectives are met, the proposal would increase the likelihood of successfully treating T1D. ● Despite much progress to generate functional islets from stem cells, some challenges remain around the need for a clinically applicable and safer transplant site and the need to reduce or eliminate chronic immunosuppression to increase the applicability of beta cell replacement to a larger number of patients with type-1 diabetes. ● The proposed technology of pluripotent stem cell-derived human islet-like organoids (HILOs) could impact that need dramatically, especially if the safe harbor feature to limit immunological attack against the grafts by expression of the immune checkpoint regulator PD-L1 proves successful. "Off-the-shelf" islet substitutes would be substantially more affordable and available to a much wider patient group than existing islet transplants or customized autologous islet constructs. ● This is a biomaterial strategy that promotes graft vascularization and reduces local inflammation, which could (if demonstrated) promote islet engraftment and long-term function in the subcutaneous site, which is highly desirable for clinical translation. ● Human stem-cell derived islet-like clusters (HILOs), if successful, could allow transplantation of almost inexhaustible islet sources without immunosuppression. ● Proposed subcutaneous transplantation technology utilizing a hyaluronan hydrogel incorporating heparin to limit scarring and VEGF to promote vascularization also could contribute to meeting the need in a cost-effective, safe way. This potentially could be a superior delivery system for islet-like structures than any that have been tried in many previous efforts. ● The co-Investigator has extensive expertise in translational engineered devices for neuropathology. This proposal is an interesting opportunity to recruit outside talent to stem cell technologies. ● It is not clear why HILOs are superior to other stem cell-derived islet products. ● It is not clear why PD-L1 overexpression would provide more immunoprotection to HILOs than other strategies. ● Until preliminary data are provided, it cannot be concluded that the proposed biomaterial strategy to promote islet engraftment in the subcutaneous site would be superior to other approaches that have already been tested successfully with islets. ● Highly relevant problem. ● Addresses a bottleneck with reasonable high chance for success. ● This is a high risk, high reward application.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 14	● The conceptual approach has been investigated for over a decade. Past emphasis was on transplantation of insulin secreting cells into cell impermanent devices but those suffered numerous technical challenges. This proposal offers an alternative approach that uses universal hiPSCs that produce immune-tolerant β cells expressing PD-L1. This approach reduces the risk of autoimmune rejection and costly personalized therapy. ● The preliminary data are compelling and supportive of the proposed project (for example, see Fig 7). ● Published data is referenced for HILOs and PD-L1-expressing HILOs. Published data is referenced and shown for biomaterial approach to promote vascularization in the brain after stroke. However, the most important data for HILOs are referenced but not shown. ● Well supported rationale. ● Team has documented important improvements to development of islet-like structures from pluripotent stem cells: 1) sophisticated use of organoid technology to generate functional, highly glucose-responsive islet-like constructs; 2) genetic engineering technology using PD-L1 to limit immune attack vs grafts; 3) improved safety feature to kill grafted cells if needed. ● Creative approach to apply methods for encapsulation and promotion of vascularization, originally developed for CNS (stroke). In principle this should work for islets, and subcutaneous implantation would have a number of advantages. Because not much

	data yet on combining the two sets of technologies from labs of the co-investigators, this aspect is high risk. However, even if it fails the HILOs represent a good translational candidate. ● One caution is that because the transplanted progenitor cells express PD-L1, the possibility of endocrine tumors arising from transplanted cells needs careful evaluation in long-term studies. The proposed use of the suicide gene system in HILOs serves as "safety switch" to limit transplanted cells, and presumably any potentially cancerous descendent cells. ● Preliminary data with hydrogels in the subcutaneous site lack controls. ● Description of biomaterial strategy is not focused: a lot of unnecessary details are provided while important experimental details are missing. ● Outstanding supporting data in high impact publications - most recent a spectacular paper from the PI in Aug 2020. The application actually does not do a great job of presenting the preliminary data and some aspects of the plan. Reviewer is giving talented but inexperienced young investigators some slack in recognizing the exceptional quality of their published work. ● The rationale seems sound.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 12	● Strong preliminary data in vivo. ● This is a concise 1 year proposal. ● Well constructed. ● Outstanding preliminary and published data. ● Fig 7 and proposed follow up studies indicate this is a well-constructed project. ● Planning and design do address key proofs of concept to advance to translation. Proposal outlines a compelling collaboration merging 1) state of the art technologies: cell biology / physiology of organoid and immunological protection with 2) nanotechnology yielding what looks like a potentially superior encapsulation system to engraft at a convenient site (subcutaneous), with VEGF added to enhance vascularization. ● A major question is whether PD-L1 expression will suffice to protect HILOs from immune rejection. Use of immunosuppressive drugs is presented as an alternative if PD-L1 does not give the desired protection -- should be clear whether this would be based on standard methods (e.g., "Edmonton Protocol") for pancreatic islet transplantation, and consider known limitations of this approach. ● The negative interactions of some components of the two systems to be merged should be assessed. For example, might components of encapsulation system such as heparin nanoparticles interfere with HILO function in glucose-sensitive insulin production? ● Simplify the plan to test the biomaterial in a mouse model and then focus on the humanized mouse. ● Some of the controls are missing. ● More detailed pitfall discussion would have helped. ● Complex product may have to overcome significant regulatory hurdles. Should bring in regulatory consultants early and begin dialogue with FDA. ● Some weaknesses in grantsmanship distract from the overall excellence of the proposal. ● Planning and design do reflect the investigators' inexperience in grant writing. The application would be improved by sticking to presentation of Milestones, separate statement of "Aims" is distracting - and in both cases the text sometimes describes activities rather than deliverables. However, objective success criteria are laid out well.
No: 2	● The overall idea and the rationale (from published work) has great potential for impact, the proposal needs to be revised and refocused as suggested. ● Aim 1 fails to describe the biomaterial approach effectively: the strategy for biomaterial synthesis reads like a paper method with unnecessary details and lack of clarity in the description of the different strategies for synthesis and characterization. ● Aim 2 is dependent on aim 1 and aim 1 will not test the capability of the gels to support islet function in the subcutaneous site. ● Because the biomaterial strategy and the HILOs expressing PD-L1 are readily available and previously reported, the proposal should be focused on testing and optimizing the biomaterial strategy in the subcutaneous site with human islets or HILOs in NODscid compared to empty gels, and evaluating whether the strategy improves survival of PD-L1 expressing HILOs in humanized mice compared to non PD-L1 expressing HILOs compared to previous data in the kidney capsule.

	• The expected outcomes and alternative strategies section would benefit from expansion; currently expected outcomes are not described and the alternative strategy for immunosuppression is not justified (no reference provided). • The potential pitfalls and alternative approaches section is very limited and should be expanded.
GWG Votes	Is the proposal feasible?
Yes: 14	• The preliminary data are strong and indicate the goals can be achieved on schedule. • The proposed team is appropriately qualified and staffed. The PI has expertise in all areas essential to the project, and runs a Stem Cell Culture facility. The co-investigator has expertise in angiogenesis in brain injury repair. Non-key personnel are appropriate. • Facilities are excellent. • The project is very ambitious for 1 year but the milestones tasks and success criteria are clearly explained. • Highly feasible, state of the art approach. • Experiments can perhaps be more streamlined. • Project is ambitious but does seem achievable. Milestones are stated more as tasks than specific deliverables. However, success criteria are clear. • PI and key investigator have published the preliminary data in high impact journals as first authors. • Given the limited expertise of the PI and key investigator in leading projects and managing grants, this application could benefit from including a letter of support from a senior investigator that will mentor the team. • This represents an exciting collaboration of two young investigators with complementary expertise in regenerative medicine technologies. The merging of their skill sets and technologies is a great strength of the application. Additional staffing requested seems appropriate to achieve the milestones. • Inexperience of the investigators in grantsmanship is obvious, but publication record over past >5 years is excellent for both. This looks like a high potential team that would benefit from some mentoring to be optimally productive and meet the ambitious but feasible goal of a true breakthrough candidate for therapy of T1D. • The plan seems ambitious, but important parts seem executable. • The budget is appropriate for the research proposed. • The project is under-budgeted for the proposed milestones and the large number of animal experiments proposed/needed.
No: 0	*none*

Application #	DISC2-12105
Title (as written by the applicant)	Human iPSC-derived chimeric antigen receptor-expressing macrophages for cancer treatment
Research Objective (as written by the applicant)	These studies will produce a new CAR-targeted iPSC-derived macrophage-based cell therapy product for treatment of refractory malignancies such as ovarian cancer.
Impact (as written by the applicant)	These studies eliminate a bottleneck in macrophage production and enable these cells to be engineered and manufactured in a standardized, off-the-shelf manner, rather than on a patient-specific basis.
Major Proposed Activities (as written by the applicant)	• Generate of human iPSCs with stable expression of tumor antigen-targeted chimeric antigen receptor constructs • Generate and evaluate in vitro anti-cancer activity of human iPSC-derived CAR-expressing macrophages (human iPSC-CARMAs) with different intracellular signaling modalities • Demonstrate efficacy of human iPSC-CARMAs against ovarian cancer in vivo • Improve efficacy of human iPSC-CARMAs in vitro and in vivo by combination with additional immune stimulating agents agents
Statement of Benefit to California (as written by the applicant)	Over 2500 women per year in California are diagnosed with ovarian cancer, and the majority of these women will die of their disease. If this cancer is not cured at an early stage, the disease will almost inevitably relapse. Therefore, new and better treatments are desperately needed. This project to use human iPSC-derived macrophages for a targeted cancer treatment provides a completely new strategy for better treatment and cure of ovarian cancer and other refractory malignancies.
Funds Requested	$250,000
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 87

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

Mean	87
Median	87
Standard Deviation	2
Highest	90
Lowest	80
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	1

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• The applicant proposes a new approach for cancer immunotherapy for solid tumors based on macrophages. If this works, it has potential to make a big impact in the field.

	• Yes. There is already evidence the macrophage CARs are effective, and this provides a potential new source. • The product could have high impact for ovarian cancer. • Given the sourcing of CAR macrophages is difficult, this could potentially hold a promising source via iPSCs. • This proposal includes a clean xeno-free source of iPSCs, and in vivo evidence of efficacy. Unclear why limited to ovarian cancers.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 14	• Yes, the rationale is sound, is based in strong science, and builds on other discoveries from the field. • Quite compelling preliminary data. • Sound rationale and well-developed techniques. • Figures 3 and 4 are impressive, and strongly suggest the proposed experiments will be successful and lead to insights required for translational use. • The strong preliminary data support their mechanism of action. • There is an assumption that genetic backgrounds are not relevant - no supportive data of HLA mismatching not being an issue are provided.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 13	• Yes, this is really nicely designed and approaches the major goals in a very systematic and logical manner. • Highly detailed plans and step by step sequence laid out, especially in Aims 3 and 4 where in vivo experiments using NSG mice are critical and use of anti-CD47 and TLR agonists that have been used clinically already on different CAR engineered cells. • Comparison to peripheral blood CAR macrophages is excellent and this should be the basis of criteria given the goal of the proposal to provide an alternative stem cell source. • Concern regarding permissive nature of NSG model. This is unlikely to provide a strong surrogate for human predictions and false impression of potential effects. • Rationale for the use of a permissive model that drives amyloid lineages and thus might not provide a good surrogate model is not provided. • Overall yes - however the animal model may not be fully representative of a patient response. • Primary and differential cancer should be tested and may be higher priority than use of anti-CD47 and TLR agonists. • A rationale for a specific cancer vs. ovarian, because it has been done before, would have increased enthusiasm.
No: 0	*none*
GWG Votes	Is the proposal feasible?
Yes: 13	• The applicant has generated compelling pre-clinical data that suggests this proposal is feasible and they will be successful. • Extremely ambitious. • The timelines are aggressive, and potentially overly ambitious to the point of being unrealistic. The proposal priorities should be streamlined if supported. • Logical, but NSG recipient may not be a good surrogate. • Milestone 4 could be streamlined. • iPSC lines, equipment, and conditions are in place given the experience and established expertise of this lab in the specific area of iPSC development to hematopoietic progeny. • Budget is appropriate, however, xenograft budget could be limited.
No: 1	*none*

Application #	DISC2-12164
Title (as written by the applicant)	Optimization of a human interneuron cell therapy for traumatic brain injury
Research Objective (as written by the applicant)	A cell therapy product comprised of inhibitory neurons that can migrate, integrate and restore neurologic function after traumatic brain injury.
Impact (as written by the applicant)	Traumatic brain injury
Major Proposed Activities (as written by the applicant)	• Examine the most effective dose and safety profile of human iPSC-derived MGE cells grafted into rodent hippocampus. • Determine whether human iPSC-derived MGE cells mature into appropriate cortical interneurons in the traumatically injured brain • Evaluate the effect of human GABA neurons on synaptic activity in the injured brain • Evaluate the therapeutic potential of human-derived interneurons
Statement of Benefit to California (as written by the applicant)	Nearly 6 million Americans - including 700,000 Californians - live with permanent physical or mental health problems resulting from a traumatic brain injury, but there are no treatments. We propose studies to create a cell therapy product that is capable of restoring neurologic function to these patients.
Funds Requested	$250,000
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 85

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

Mean	85
Median	85
Standard Deviation	2
Highest	87
Lowest	80
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	12
(1-84): Not recommended for funding	2

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 12	• Traumatic brain injury (TBI) certainly represents an important unmet medical need. This is a frequent type of neurological injury, and we do not have satisfactory approaches for treatment. • Traumatic brain injury is a tremendous problem. • Impact would be significant • Excellent investigator. • TBI is a major need for an important condition.

No: 1	*none*
GWG Votes	Is the rationale sound?
Yes: 12	• The careful development of human MGE progenitors for transplantation-mediated treatment of TBI offers a scalable approach to the generation of cells that offer promise to be effective in this process. • Well studied cell population. • The behavioral tests conducted provide promising results in respect to behaviors that are interpreted as being relevant to memory and fear conditioning. • The effects on seizure frequency are quite interesting, • The mechanism of action seems clear and supported by preliminary data.
No: 1	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 12	• This is a very well articulated research plan, with a great deal of work and thought going into the scalable production of human MGE progenitor cells. • The rationale for this proposal is scientifically sound, and is based both upon an understanding of neuronal function in vivo and on a great deal of preliminary research demonstrating the potential value of this approach in relevant murine models. • Excellent preliminary data and promising behavioral analysis. • Very minor experimental concerns. • No concerns noted.
No: 1	*none*
GWG Votes	Is the proposal feasible?
Yes: 12	• There is a careful development of strategies for developing an MGE cell therapy for TBI. • Scalability might be an issue (but that is the case for nearly all approaches). • Translational path provided.
No: 1	*none*

Application #	DISC2-12172
Title (as written by the applicant)	Combating COVID-19 using human PSC-derived NK cells
Research Objective (as written by the applicant)	We propose to generate NK cells with enhanced immunity from gene-edited human PSCs and use the resultant NK cells to kill SARS-CoV-2-infected cells to combat against COVID-19.
Impact (as written by the applicant)	The use of gene-edited hPSCs as a source for genetically engineered NK cells will allow us to generate effective immunotherapy for COVID-19 that has no approved treatment thus far.
Major Proposed Activities (as written by the applicant)	• Generation of gene-edited hPSCs • Differentiation of hPSCs into NK cells • Characterization of hPSC-derived NK cells • Testing the effect of hPSC-derived NK cells on SARS-CoV-2-infected cells
Statement of Benefit to California (as written by the applicant)	Many confirmed cases of COVID-19 (>600,000) have been reported in California, which have resulted in substantial (>10,000) deaths. Besides the tremendous emotional and physical pain that this disease inflicts on families, it produces a huge medical and fiscal burden and halts economic growth in California. Thus, there is a real need to develop a strategy of treatment for this disease. Our study will address the needs by developing a highly effective hPSC-based cell therapy for COVID-19.
Funds Requested	$249,998
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 85

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

Mean	85
Median	85
Standard Deviation	4
Highest	90
Lowest	80
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	8
(1-84): Not recommended for funding	7

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• Given the need for further SARS-CoV-2 antivirals this project could be highly significant. Further, the model has broad applicability in research in this area which increases the overall impact. • Basic immunology of SARS-CoV-2 and cell engineering for NK cells are both valuable contributions. • Yes, but the project oversells the likelihood of this turning into a cell product. From a basic point of view, though, the project is significant. • Will lead to new insights.

	• Yes, but really this proposal is for the next pandemic, and not this one. Hopefully. • There are likely contributions to fundamental biology and help with our preparedness with our next pandemic.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 14	• The investigators present a strong rationale that their model combined with drug screen will be productive and beneficial to the field. • Yes, it is a discovery project so there is some risk but the rationale is plausible. • NK seem critical. • Good to generate NKs for this purpose. • No concerns with the rationale.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 14	• The project is well designed with appropriate milestones. It may be somewhat overly ambitious, but the investigators have thoughtfully considered markers for success. • Yes, all technical details are very solid and likely to lead to clear results. • Good experimental design, well responsive to previous critiques. • Improved application, responsive changes. • The rationale seems solid with good preliminary data.
No: 0	*none*
GWG Votes	Is the proposal feasible?
Yes: 14	• Given the proven success of the investigators and the high development of the models plus the robust preliminary data, this project seems highly feasible. Additionally, this team has had a high degree of success in this area in the past and the facilities and investigators are all top notch. • Yes, especially as the CRISPR works already. • Reasonable time line. • Experienced investigator and good environment. • The team seems well qualified to execute the plan.
No: 0	*none*

Application #	DISC2-12126
Title (as written by the applicant)	The First Orally Delivered Cell Therapy for the Treatment of Inflammatory Bowel Disease
Research Objective (as written by the applicant)	The goal of this project is to develop the first ORAL cell therapy as a breakthrough treatment for inflammatory bowel disease [IBD].
Impact (as written by the applicant)	We engineered a new way to deliver cells ORALLY instead of by injection. In doing so, we will better reach the inflamed tissues and provide a much-needed new treatment for those afflicted with IBD.
Major Proposed Activities (as written by the applicant)	• We expect that from these studies an optimal dose and dosing regimen for the oral cell therapy will be established and will help build our clinical target product profile. • We expect that we will further characterize the anti-inflammatory mechanism of action of the oral cell therapy. • We will also establish the biodistribution of the orally delivered cells to further gain support for advancement of our breakthrough IBD therapy towards clinical studies. • We will collect all of the information needed to request an FDA INTERACT meeting.
Statement of Benefit to California (as written by the applicant)	The current standard of care works in only a third of the inflammatory bowel disease [IBD] patients. IBD incidence is growing in California and elsewhere, and there is no known cure. Cell-based therapy is considered the next generation treatment approach for IBD. An orally delivered cell therapy simultaneously solves some of the hurdles of this promising industry while offering a much needed novel therapeutic to IBD patients.
Funds Requested	$249,000
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 85

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

Mean	83
Median	85
Standard Deviation	5
Highest	90
Lowest	70
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	8
(1-84): Not recommended for funding	6

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 12	• The proposed technology will likely result in a candidate that could impact an unmet medical need.

	• This is a compelling proposal for a cell therapy candidate where human progenitor cells are incapsulated in an engineered matrix for oral delivery of mesenchymal stem cells (MSC) to treat inflammatory bowel disease (IBD). • If successful the therapy would greatly improve patient care for IBD, and validate a vehicle for oral delivery of other stem cell applications. • The key personnel have extensive expertise in translational research and medicine. • High unmet need. • MSC cells have already been shown to be are a suitable therapeutic approach but delivery method is not optimized.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 12	• The project is uniquely enabled by the combined technical advances of engineered capsules for storage and oral delivery of therapeutic MSC to treat IBD. • The concept of oral delivery of MSC in a protective capsule for therapeutic colonization of the gut is straightforward. The application places heavy emphasis on the viability of the MSC in their engineered matrix capsules. However, more traditional routes of therapeutic delivery are presented as alternative approaches. • The first figure indicates that MSC therapy alleviates disease in Crohn's-like ileitis model in mice. However, the cells were locally delivered by IP injection. • The cells remain viable even when stored at ambient temperature for periods of up to a month but no data was shown to explicitly present this result. • No preliminary data to show MSC can colonize the gut via oral delivery in capsules but conducting those preliminary tests is one purpose of this funding mechanism. • Oral delivery of therapeutic mammalian cells is safe in minipigs - but are the cells now biologically active in the gut? These preliminary data would greatly increase enthusiasm for this project for subsequent translational studies in clinical trials. • Builds on comprehensive data. • Project description would have been clearer had the Figures been numbered.
No: 1	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 11	• The proposal describes preclinical studies in mice. The next objective in future studies is to validate the approach in large animals. The project is then ready for clinical trials. A key personnel states in a letter of collaboration and support that clinical trials can be conducted at their institution. • This a well-constructed, quality project, consistent with the expertise of the PI and research team. • If the engineered matrix capsules fail to perform, an alternative approach will be pursued of delivering MSC by suppository. The results of the first figure (MSC therapy alleviates disease in Crohn's-like ileitis model in mice) would suggest this alternative approach would work. • The timeline completes preclinical studies in mice, including all studies necessary to progress to a final round of preclinical studies in large animals. • Well established methods. • Dose and delivery will be established. • Powerful model system in place.
No: 2	*none*
GWG Votes	Is the proposal feasible?
Yes: 11	• Comprehensive application with clear milestones. • Strong preliminary data. • Milestone 2 proposes to "nail down the anti-inflammatory mechanism of action of the OCT and establish the biodistribution of MSCs". This is over ambitious, as it represents years of work. Inflammatory networks are exceedingly complex and context dependent. Nevertheless, enough can be learned to support the present proposal and seed preliminary data for future funding by other basic research granting mechanisms. • Applicant investigators are an excellent team. One has expertise in translational applications of MSC technology and founded several biotech companies. Another has expertise in MSC therapy for inflammatory bowel disease. • The team has outstanding resources and expertise.

	• Appropriate funding is requested. • Alternative approach is discussed but not incorporated.
No: 2	*none*

Application #	DISC2-12130
Title (as written by the applicant)	Transplantation of Pluripotent Stem Cell Derived Microglia for the Treatment of Adult-onset Leukoencephalopathy (HDLS/ALSP)
Research Objective (as written by the applicant)	We propose to investigate the transplantation of pluripotent stem cell derived microglia as a potential therapy for the devastating neurological disease; Adult-onset leukoencephalopathy (ALSP/HDLS).
Impact (as written by the applicant)	The most immediately impacted condition will be ALSP. However, further examination of the safety of human microglial transplantation will have broad implications for many neurodegenerative disorders
Major Proposed Activities (as written by the applicant)	• We will differentiate the human embryonic stem cells line ESI-017 into microglia, the primary immune cell of the brain. • We will assess the purity of stem cell derived microglia by examining multiple markers for microglia and stem cells. We aim to achieve greater than 99% purity. • We will utilize single cell RNA sequencing as a sensitive method to determine whether any contaminating pluripotent stem cells remain following microglial differentiation. • Using specialized mice that develop ALSP pathology and allow human cells to be transplanted, we will engraft human microglia into the brain. • We will allow mice to age for 3 months and then use a series of tests to examine the impact of microglial transplantation on motor and cognitive function. • We will examine the impact of human microglial transplantation on ALSP-associated neuropathologies. We will then report our results and schedule a discussion with the FDA.
Statement of Benefit to California (as written by the applicant)	Adult-onset leukoencephalopathy (ALSP) is a neurological disease that effects patients during the prime of their lives. Although rare, ALSP represents the clearest example of a 'microgliopathy', a disorder that affects microglia, the immune cell of the brain. As microglial dysfunction is implicated in virtually all neurological disorders, the examination of stem cell-derived microglia to treat ALSP could provide important insight into many of the neurological diseases that affect Californians.
Funds Requested	$249,968
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 85

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

Mean	82
Median	85
Standard Deviation	5
Highest	90
Lowest	75
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	7
(1-84): Not recommended for funding	6

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 13	• This is a basic biology question that seeks to understand the role of microglia in neurodegenerative disorders. • The focus on Adult-onset leukoencephalopathy (ALSP) a rare progressive neurological disorder caused by dominantly inherited mutations in the gene CSF1R that is critically important for the function and survival of microglia, and is a logical starting point. • Adult-onset leukoencephalopathy (ALSP) is an unmet medical need. • Microglial transplantation could have major impacts for these patients. • Human iPSC-derived microglia are a valuable source of transplantable cells in the adult mouse brain. The procedures and requirements for successful microglia engraftment in the mouse brain can be potentially translated for transplantation in human beings, though transplantations studies have not yet performed in large animal models to assure the translational potential of this approach.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 13	• Yes, the concept is straightforward. Generate patient derived iPSC cells, differentiate them into microglia, correct the defect via CRISPR and transplant into patients. • The rationale of this application is very strong, based on solid work and previous achievements. • Preliminary data are extensive, of good quality and extremely convincing. This study is based on the innovative work of this group who was first in setting an efficient protocol for microglia generation from human iPSC and demonstrate their integration efficiency after brain transplantation. • Normalization of microglia in ALSP could provide disease altering therapies. Using ALSP as a proof of concept model is reasonable. • The project is based on the proposal that transplantation of microglial cells might be beneficial in ALSP. As this disease arises from a genetic microglial dysfunction, this is not unreasonable. • Cell replacement aims seem sound.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 8	• The proposal is well delineated with two related aims. • The ALSP mouse model lacking endogenous microglia is ideal to assess the engraftment potential and beneficial effects of the transplanted human microglia. However, most of the other diseases remain with dysfunctional endogenous microglia and, thus, the approach proposed herein can not be generalized. • The applicant rightly points out that genetic manipulations in microglia are challenging and thus proposes to use WT microglia. This negates the power of patient derived allogenic transplants. No future direction is provided to overcome this hurdle. • That said, there are no preliminary data that support the idea that this would work. They can make microglia, but there's no demonstration that transplanting human cells would have any therapeutic benefit in an ALSP model. • Due to the importance of microglia as antigen presenting cells, one would want to see evidence that haplotype matching is not necessary, or plans for generating the many different types of microglia that would be required for haplotype matching. • Potential problems have been highlighted with reasonable solutions and alternatives. Cognitive and motor functions are assessed with a limited battery of behavioral tests. Electrophysiological recordings are mentioned but not further delineated. They would help in validating the functional rescue by the transplanted microglia.
No: 5	• The growth conditions for the cells are not well considered.
GWG Votes	Is the proposal feasible?
Yes: 9	• Reducing levels of the protein have already been shown to be effective. It is not discussed why microglia itself, that cannot be corrected would provide a better therapeutic target than reducing protein levels. • Highly feasible and good preliminary data.

	• The milestones and outcome of the project are likely to be reached based on the expertise of the group and the large preliminary data already collected in this line of research. • Highly qualified, although future development and clinical application need to be better considered. • This project is dependent upon making human microglia for transplantation, for which this group is a leader. • The group has pioneered this approach providing valuable contributions to set up protocols for generating human microglial-like cells and assess their in vivo potential. • The group is well equipped with all the necessary infrastructure to carry out this project. The lab is embedded in a very stimulating environment with experts in both pre-clinical and clinical studies. • The budget is fully consistent with the proposed load of work.
No: 4	• The microglia transplantation experiments do not seem as straightforward as they propose.

Application #	DISC2-12098
Title (as written by the applicant)	Glial-restricted neural progenitor cells as a treatment for Rett syndrome
Research Objective (as written by the applicant)	Glial-restricted neural progenitor cells derived from human pluripotent stem cells
Impact (as written by the applicant)	Rett syndrome and potentially other neurodevelopmental and neurodegenerative disorders
Major Proposed Activities (as written by the applicant)	• Characterization of the candidate glial-restricted progenitor stem cells • Transplantation in human Rett syndrome brain organoids • Transplantation in the brain of a mouse model for Rett syndrome • Measure the cellular, physiological, behavioral and survival impact of the cell transplantation • Prepare and organize the next steps in large animals
Statement of Benefit to California (as written by the applicant)	Brain disorders are responsible for more years lost to disability than any other medical condition. Cell therapeutics pioneered to understand and treat rare single-gene disorders such as Rett Syndrome will provide the tools and methods that will ultimately be used to address the more common complex brain disorders. In fact, the proposed gene mutations are not restricted to Rett syndrome but also autism spectrum disorders, affecting 1 in every 54 births worldwide.
Funds Requested	$250,000
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 80

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

Mean	80
Median	80
Standard Deviation	11
Highest	95
Lowest	50
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	7
(1-84): Not recommended for funding	8

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 12	• Disease is devastating in some patients (mainly males) with no cure. • Clearly very high risk, high reward type of proposal. A reviewer made a compelling argument that the preliminary data are exceptionally strong, and it is worthwhile to test cell transplantation in an animal model.

No: 2	• This proposal is at its very early stage in research development and stands as a proof-of-concept study which maintains for the moment a limited potential for granting a future development as a therapeutic strategy for clinical applications. • The approach has low translational potential.
GWG Votes	Is the rationale sound?
Yes: 11	• Re-expression of the gene preferentially in astrocytes in globally gene-deficient mice significantly improved locomotion and anxiety levels, restored respiratory abnormalities to a normal pattern, and greatly prolonged lifespan compared to globally null mice. • The study found that simply promoting BDNF transport, without increasing BDNF production, was sufficient to restore synaptic connectivity in the corticostriatal network and to improve the phenotype and survival of knockout mice. • BDNF as a possible therapeutic contribution for astrocytes should be considered.
No: 3	• Preliminary data and previous literature show that RTT astrocytes have a detrimental non-cell autonomous effect on neurons. However, to which extent gene reintroduction in astrocytes will rescue cognitive and behavioral deficits remains to be fully validated. Only one report assessed this issue in RTT mice years ago and more investigations are required to extend these findings. • RTT astrocytes encode negative cues for neuronal function and survival. Data presented herein are exclusively on in vitro neuronal cultures that represent a simplified model with low predictability for more complex brain functions and cognitive performance. In contrast, a large body of evidence in the literature shows that deleting MeCP2 in neuronal subtypes is sufficient to cause multiple brain deficits largely comparable with those in full mutant mice. • Re-establishing gene function in astrocytes can be obtained by reintroducing a functional copy of the gene by viral therapy. This last approach has important advantages with respect to a stem cell-based therapy in terms of feasibility, safety and overall costs. This was not discussed in the application. Thus, to what extent healthy astrocytes can rescue severe neuronal deficit in RTT remains to be explored in more detail. • The organoid cultures do not seem necessary and the mechanism of action is unclear.
GWG Votes	Is the proposal well planned and designed?
Yes: 10	• Solid preliminary data. • No concerns noted.
No: 4	• The experimental work is well planned as far as it concerns applications in mice. However, the study is limited to assessing basic aspects of neuronal morphology. There is some need to go beyond morphological assessments and move to more functional assessments to measure functional parameters and their behavioral correlates. It would be advantageous to include gene expression studies on RTT neurons with healthy or RTT astrocytes. • The transplantation of human GRNPCs is feasible only at neonatal stages to enable the human astrocytes to outcompete the mouse endogenous ones. This time schedule is impractical for translational applications in RTT patients. Neither alternatives nor contingency plan elaborate on this crucial issue in the proposal.
GWG Votes	Is the proposal feasible?
Yes: 13	• Very convincing. • The team is well staffed and would likely execute this project well.
No: 1	• The plan is overall logically designed with in vitro and in vivo activities running in parallel. The total amount of workload is significant. Beyond the PI, only a second key research assistant is listed. It is not mentioned how this large amount of work would be further subdivided between technicians and students. • The team has a strong expertise in stem cell biology and RTT pathophysiology. They have contributed with key advances in modeling RTT with human stem cell-based models. This application take full advantage of their expertise and previous achievements. • The PI is a fully established scientist with a very active and successful lab. They are fully equipped for conducting this work and have well structured institutional facilities for advanced imaging and genomics. • The budget is fully justified for the presented experimental plan and necessary workload.

Application #	DISC2-12123
Title (as written by the applicant)	Rejuvenation of intervertebral disc with iPSC-derived notochordal cells to treat low back pain in wild type and diabetic rat model
Research Objective (as written by the applicant)	We aim to develop a cell therapy for discogenic pain in patients with and w/o type 2 diabetes addressing the cause for diabetes-driven back pain and treating the intervertebral disc tissue.
Impact (as written by the applicant)	The study will develop a combined therapy to treat both diabetes-induced disc degeneration and discogenic pain in general
Major Proposed Activities (as written by the applicant)	• Determine the therapeutic potential of induced pluripotent stem cells in a non-diabetic rat models of disc degeneration and discogenic low back pain • Determine the therapeutic potential of combined small molecule and stem cell treatment in a diabetic rat model of disc degeneration and discogenic low back pain
Statement of Benefit to California (as written by the applicant)	"Doc, my back is killing me!" This is one of the most common complaint heard by Californian primary care providers. Diabetes has reached epidemic proportions, affecting over 25.8 million in US. CBC reports that Californians suffer from the disease in even higher prevalence (9.7% as opposed to national 8.5% in 2016). It was shown to be a huge risk factor for back pain. In this study we will develop the unique therapy to treat back pain in general population and specifically in diabetic patients
Funds Requested	$250,000
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 80

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

Mean	77
Median	80
Standard Deviation	7
Highest	85
Lowest	60
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	3
(1-84): Not recommended for funding	12

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 13	• Low back pain (LBP) affects 80% of adults; intervertebral disc (IVD) degeneration causes 40% of all pack pain and depends on processes in the nucleus pulposus (NP); current pharmacological and surgical treatments focus on symptom alleviation and don't target the disease. • Cell therapies for IVD include MSCs injection in the NP but they induce ossification while autologous NP injection halt degeneration but sourcing is an issue. Rejuvenating NP cells

	with stem cells could stop NP degeneration and circumvent sourcing issues of transplantation. • Type 2 Diabetes Mellitus (T2DM) has been identified as a clinical risk factor for spinal disease, including IVD degeneration. Daily anti-AGE (advanced glycation end products) drug treatment showed promising results in phase 2 studies of patients with T2DM and protective effects on intervertebral discs in diabetic mice. • Injecting iPSC-derived notochordal cells within a micro-hydrogel delivery system may rejuvenate IVDs, attenuate disc degeneration and prevent discogenic pain in non-diabetic and diabetic individuals suffering from IVD disease. • Increased incidence of diabetes among patients undergoing surgery for disc disease does not suggest that diabetes affects IVD degeneration but more likely that IVD degeneration and resulting mobility decrease may affect diabetes incidence. • Novel and well rationalized approach. • This treatment seems like a conditioning treatment but may have promise.
No: 1	• The proposal to use iPS derived notochord cells to repair the intervertebral disc is a good one with some good preliminary evidence. However the proposal is greatly weakened by its focus under Aim 2 of the treating intervertebral disc disease in a diabetic setting using a combination therapy.
GWG Votes	Is the rationale sound?
Yes: 11	• The basic rationale is sound but the evidence base for focusing on diabetes is weak. • Published data support the overall hypothesis. • No concerns with the rationale. • Strong preliminary data in small and large animal models of IVD degeneration support most of the proposed project. • Figures are too crowded with dense information and in some instances critical information are missing. For example, preliminary data for feasibility of biobehavioral tests in fig.2F lack important information. • No preliminary data are shown to support feasibility of the imaging of the cells by intradisc injection. • Long-term stability of Dil labeling for the cells has not been demonstrated.
No: 3	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 7	• Very detailed description of experimental procedures. High quality preliminary data and clearly identified tasks to complete milestones. • The in vivo preliminary data is strong. • Rationale for moving from pig model to rat model is provided. • The rat models enable a functional read out of pain. • Measured quantitative outcomes for each experiment are largely missing. • Aspects related to bio-material are poorly discussed. • The biomaterial is not well described. • The autologous or allogeneic strategy is not well described. • Both potential pitfalls and alternative strategies are described but with minimal details. • The plan for translation of the product is missing
No: 7	• The combination of notochord cells delivered in a gel together with a drug is over-complicated. The data emerging from this complex design will be difficult to evaluate and the eventual therapeutic will be difficult to take through a regulatory pathway. • Seems a major concern is with use of the diabetes model.
GWG Votes	Is the proposal feasible?
Yes: 11	• Aim 2 might be not necessary for proof of concept and diabetes model lacks clear rationale. • Advancement to therapeutic translation questionable and not discussed. • Feasibility of the bioluminescent approach not well evaluated.
No: 3	• The application is very dense and the project is overambitious for the one year timeline. • Aim 1 is feasible but aim 2 is very challenging and probably not feasible. • Aim 2 should be eliminated. • Milestones are feasible, but the aims do not seem feasible. • The team has access to iPSCs, imaging and genomic core facilities. • Very limited budget for such an ambitious project.

Application #	DISC2-12155
Title (as written by the applicant)	iPSC-based secretomes for treatment of pelvic organ prolapse
Research Objective (as written by the applicant)	The candidate consists of proteins produced by human iPSC-derived smooth muscle cell progenitors
Impact (as written by the applicant)	This is a non-surgical treatment for pelvic organ prolapse. Current treatment for this debilitating condition is surgery involving implantation of synthetic meshes which has many complication.
Major Proposed Activities (as written by the applicant)	• Produce and bank sufficient candidate therapy from smooth muscle cell progenitors differentiated from human iPSCs to support Activity 2 • Treat the animal model with the candidate to confirm proof of concept and reproducible disease modifying activity using iPSC lines from three patients • Evaluate the tissue effect and mechanism of action of the candidate on the damaged vaginal tissues
Statement of Benefit to California (as written by the applicant)	It will offer Californian women suffering from pelvic organ prolapse a safe, non-surgical treatment. More importantly, it can be a therapy for prevention of future prolapse because it can be used to enhance healing of the vagina after childbirth. This candidate can be produced and stored which will allow for rapid access and multi-dose treatments. It is injected into the vagina in the clinic which will increase access to care for underserved populations.
Funds Requested	$250,000
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 80

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

Mean	76
Median	80
Standard Deviation	8
Highest	85
Lowest	60
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	3
(1-84): Not recommended for funding	12

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 12	• Pelvic organ prolapse is a major problem. Surgical interventions are currently the only effective treatment. Many women suffer from this condition. Latina women suffer at a high rate and are a significant portion of the California population. • Pelvic organ prolapse represents a significant health problem and the current treatment options are limited.

	• A stem cell treatment derived from the supernatant of cultured stem cells is much more translatable and scalable than a treatment requiring stem cell transplantation. • 45% of women over 45 years of age are affected and the problem is understudied. • There is currently no good therapeutic approach. • If successful, one could envision the proposed approach could lead to the development of a new treatment option. • If the approach works, a paracrine approach would be a real option for approaching the disease. • The need for this work is high but the path to the clinic seems long and this is very early stage.
No: 3	• The PI has expertise in the generation of iPSC-derived muscle smooth cells, and has been funded by CIRM for testing the therapeutic application of cell replacement in urinary incontinence. Here, the PI proposes to validate this strategy on pelvic organ prolapse. However, the PI now proposes to use the conditioned medium from iPSC-derived muscle smooth cells. • This project is at very early stage as the investigator will need to determine if there is any therapeutic benefit for pelvic organ prolapse, and if yes, much more work will be needed to understand mechanism, how reliable and safe are secretomes generated from different iPS cell lines, as well as long-term effects. • It would have been nice to see progression for the previous proof-of-concept studies for urinary incontinence. Did the previous work evolve to IND-enabling studies?
GWG Votes	Is the rationale sound?
Yes: 11	• The overall study design is well developed and supported by preliminary data. • A previous paper by the authors shows in rodents that human stem cells improve function. Seemingly, some of this improvement must come from action at a distance by the human stem cells, as rat proteins showed increased expression. This paper received national attention in the urology community, urging more research. • Preliminary data is presented on the overall techniques, the proposed cell lines and the animal model. • Given that the research may not be quite ready to move into humans, additional research in a model organism is the correct next step. • It makes sense to test whether a secreted factor from the stem cells could be responsible for improved pelvic connective /muscle tissue function. • The paracrine effects provide a good rationale. • Some reviewers wanted to see more of a specific mechanism proposed, such as specific proteins or factors hypothesized to be responsible for the mechanism of action. • Providing a biological support structure (rather than operative inserted mesh structures) is novel and makes sense.
No: 4	• The idea of cell replacement seems to have been abandoned with no clear rationale in the project. In Vision for Progression, the PI justifies that secretomes may have less regulatory hurdles than cell replacement. While this may be true, superior or at least equivalent therapeutic benefit needs to be demonstrated.
GWG Votes	Is the proposal well planned and designed?
Yes: 10	• Overall, the proposal is well developed and clearly presented. • Published data from this group supports a secretome approach. • The cell lines which are used in this study are established, although a justification of the lines is not well presented. Why were lines from post-menopausal women selected? • The experimental procedures are well described. The animal model is established. • Power calculations are (fairly) detailed and appropriate. • Alternative strategies and pitfalls are well presented. • Lack of detail on the approach makes interpretation difficult ... ie, how much media is injected, is stage of disease important...? • The proposed underlying mechanisms is due to paracrine effects of the utilized cells. There is only a limited effort to dissect or elucidate the underlying mechanisms. What components might be responsible and what is the mechanism? The proposal appears in that aspect very descriptive.
No: 5	• Some preliminary data are provided but limited information is provided on figure legends and text, which makes interpretation of the results difficult (Fig. 6, for example). It is also not clear how experiments were (and will be) performed. How much conditioned medium will be injected?

	• It is described that "our preliminary data revealed improved contractility of the pSMC treated bladder compared to the radiated-sham treated bladder (Fig. 12)". There is significant variability in these results and no statistical analysis is provided. Therefore, I am afraid some conclusions are overstated. • Variability in the secretomes could be high.
GWG Votes	Is the proposal feasible?
Yes: 12	• The project has a modest set of aims, all of which are achievable in the proposed timeframe. Given the limited budget, these aims are very appropriate. • The team has the knowledge to perform the proposed work, but timeline is not realistic. The first 6 months (half of the duration of the project) will be spent differentiating the iPS cells into smooth muscle and collecting conditioned medium. Only at month 4 they will begin pilot proof-of-concept studies. • The methods and experimental models are developed and established in the lab. • Early stage research that will not likely lead to a pre-clinical product but the research needs to be done. • The team is very strong. Previous performance on CIRM funded grants is excellent. • This is a strong group and likely could execute the approach. • The team is highly qualified. • The resources and budget are appropriate.
No: 3	*none*

Application #	DISC2-12145
Title (as written by the applicant)	Engineering MSC formulation to improve survival and efficacy in vivo
Research Objective (as written by the applicant)	Mesenchymal stem cells work well to heal many damaged tissues in animal models, when used fresh. In human trials they are freeze-thawed and damaged.We are restoring the cells' fitness to survive.
Impact (as written by the applicant)	MSCs currently stored as frozen products could be augmented with the molecules we are validating and have their potency restored by being shielded from the human body.
Major Proposed Activities (as written by the applicant)	• For Milestone 1 we will add the recombinant molecules to frozen/thawed human MSCs and perform a battery of testing, in the dish and in mice, to show enhanced potency, fitness and survival. • For Milestone 2 we will determine whether transiently adding a gene to the cells (that will go away after a week) before freezing can make them resistant to the negative effects of freeze-thawing.
Statement of Benefit to California (as written by the applicant)	CIRM has invested in MSC therapies and we seek to improve the outcomes of those clinical trials for all Californians. It wasn't initially understood that MSCs - large adhesion-dependent cells - do not respond to freezing, thawing, and injection in the same way as hematopoietic, or blood-forming stem cells. MSCs put "flags" on their surface that target them for rapid destruction by complement-mediated lysis, so they can't do their job. Our work will shield MSCs from destruction to improve outcomes.
Funds Requested	$249,998
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 75

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

Mean	75
Median	75
Standard Deviation	8
Highest	87
Lowest	60
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	2
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 13	• If the preconditioning or modification of MSCs improves engraftment, it could impact numerous indications under study. There would still be much work to be done before clinical use. Homing and safety, for example, would need to be studied using the modified cells. However, positive results from this application would lead to promising directions for the future.

	• Combating inflammatory activation in freeze-thawed MSCs is a problem that needs a solution for being a viable therapeutic agent. • This work could be quickly applicable to a wide range of MSCs. • Whether the methods in the application would be truly feasible for widespread commercial use is questionable. The need for investigational pharmacy able to do cell processing significantly limits the use of the product, and how many people could get access. However, over time the methods could hopefully be improved and simplified to be closer to a bedside procedure.
No: 1	• This proposal might lead to methods to reduce adverse events upon transplantation of MSCs. This research could lead to methods that make cellular transplantation safer in patients by mitigating the risk of complement activation and coagulation. • The proposed research will really determine aspects of mouse inflammatory and coagulation responses to human cells. There is concern that these findings will not translate to a human system.
GWG Votes	Is the rationale sound?
Yes: 9	• The preliminary data does show that cultures of revived MSCs (from cryopreservation) in 1% oxygen prior to engraftment improves the engraftment efficiency substantially. However, it is not clear how this relates to the proposed molecular and genetic modification in the research plan that aims to improve acceptance of the grafted cells. • Incremental step that is focused on improving the persistence of cell presence. • The data provided, an increase from about 1% to 10% cell persistence, is promising. • Though the grant poses the hypothesis that much of failed engraftment or complications are due to TF and inflammation, there is scant evidence to support the proposed mechanisms in the preliminary data. • The grant lacks preliminary data to indicate the complement-mediated destruction of MSCs is a major problem, though this is a major goal to be addressed in the research plan. • The host response in an animal model may not correlate to the human. • The animal work could be a useful screen of the different strategies. The key to success is whether the complement-mediated mechanism is conserved between mice and humans. • Pro survival factors are not sufficiently described in the preliminary data, though they seem to be important. The precise identity and usage of the factors is not presented.
No: 5	• Significant question about relevance of the mouse model to behavior of MSCs in humans.
GWG Votes	Is the proposal well planned and designed?
Yes: 8	• Well trained investigators.
No: 6	• There are more efficient study designs. There are many experimental groups (e.g. Table 2). While the applicant mentions statistical analysis will be performed, it does not appear to include correction for multiple comparisons. I think it's reasonable for this early stage work, but it is a stretch to imply that they would be able to clearly interpret that large number of groups with the statistical methods they describe. • The work should focus more clearly on a host response within humans, potentially through ex vivo systems. • It is not clear whether engineered or treated MSCs that engraft and resist inflammatory and complement resistance in mice will behave in the same way in humans, as the human inflammatory system will not be assessed using the proposed experiments. • It is not clear that intramuscular injection of human MSCs into immunocompromised mice is an adequate model in which to validate activity as a step leading to the use of MSCs in humans. Presumably, human engraftment of MSCs would be achieved by veinous routes rather than intramuscular injection. • The use of human blood-based coagulation assays helps somewhat in assessing the utility of treating MSCs in a human system, though this approach will not address complement concerns or inflammation concerns. • The research plan needs to be more molecular. • The two components of the research plan that will look at lung damage (10 and 11) are surprising and little background is provided to justify why these are relevant. • They plan to try two preconditioning agents and transiently engineering. The description of the plan could have been clearer and more specific on exactly how many agents will be tried. It was somewhat vague.

	• The grant mostly lacks a discussion of expected results and plans for alternative measures should difficulties be encountered.
GWG Votes	Is the proposal feasible?
Yes: 10	• The milestones are well defined and are achievable and consistent with the timeline provided. • This is a well-qualified team that has published multiple papers on human MSCs. This team seems well positioned to complete the proposed work. • This team has access to all required resources and instrumentation necessary. • The budget seemed low - certainly very reasonable for the number of mice in the experimental design.
No: 4	• Preliminary data are provided that support the approach although effect seems mild. • Too many animals groups impact feasibility. • The later milestones are too ambitious.

Application #	DISC2-12121
Title (as written by the applicant)	Targeting Mesothelioma Using HSC-Engineered Off-The-Shelf CAR-iNKT Cells
Research Objective (as written by the applicant)	HSC-engineered allogeneic mesothelin-targeting CAR-iNKT (MCAR-iNKT) cells
Impact (as written by the applicant)	treatment for mesothelioma
Major Proposed Activities (as written by the applicant)	• Milestone 1. Production of allogenic MCAR-iNKT cells • Milestone 2. Characterization of allogeneic MCAR-iNKT cells • Milestone 3. Delivery of the new therapeutic candidate
Statement of Benefit to California (as written by the applicant)	Mesothelioma is an aggressive cancer caused by exposure to asbestos fibers; California is the state with the highest number of mesothelioma deaths at US. Despite the existing treatments, mesothelioma remains incurable with an life expectancy of 12-21 months after diagnosis. New therapies are therefore in desperate demand. The proposed project can potentially lead to a novel off-the-shelf cell therapy for mesothelioma, that can save lives and/or improve life qualities of mesothelioma patients.
Funds Requested	$250,000
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 70

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

Mean	71
Median	70
Standard Deviation	1
Highest	75
Lowest	70
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 10	• The product is proposed as a therapy for mesothelioma. This disease is usually lethal with few approved treatment options, and the development of a useful therapy would be significant. • Current engineered iNKTs of this type have not been created from Human HSCs for Mesotheliomas. The need is large with 3K cases per year, and growing to 20M given the

	latency from asbestos exposure. California's greatest deaths from cancer with a 12-21 month survival post diagnosis. Need is high. • An off-the-shelf mesothelin specific cell therapy could be very impactful for patients. • Since mesothelin is expressed in many cancers, it is possible that the product could be useful in other diseases. • CAR-T is in development for the same target and disease; the rationale for the need for an allogeneic product is relatively weak. • Not very novel.
No: 3	*none*
GWG Votes	Is the rationale sound?
Yes: 7	• CAR T cells are effective and approved for non-Hodgkin's lymphoma and anti-mesothelin CAR-T cells can produce responses in mesothelioma in combination with anti-PD1. Therefore, there is a rationale for T cells targeting this antigen in mesothelioma. • iNKT cells have demonstrated clinical activity comparable to CAR T cells in heme malignancies in very small trials. Therefore, it is possible that CAR-iNKT cells will be effective in mesothelioma. However, it is not clear that there is any efficacy benefit over CAR-T cells. • Early CAR iNKT cell trials have demonstrated good safety profiles, but these studies have been small. Therefore, it is possible that these cells have a toxicity advantage over CAR T cells. • The comparable efficacy of CAR iNKT cells and CAR T cells may be identified through the later stage projects funded by CIRM. It would be reasonable to wait for clinical data using these products to validate the utility of CAR-iNKT cells in general. • The ability to produce CAR iNKT cells from UCB cells is convincing. • From the data provided for BCMA targeting iNKT cells it is not clear that the HLA-E edited cells provide any additional value. • Mesothelin-targeting CAR iNKT cells have already been produced and characterized both in vitro and in vivo by the group. • Many of the planned engineering steps have already been accomplished in the development of other products and repeating those studies seem superfluous in this proposal.
No: 6	• Strong rationale given iNKTs are effective and current alternative to CAR-Ts that are experiencing limitations, especially in solid tumors. • There is no clear scientific rationale for why a CAR-iNKT cell based therapy targeting mesothelin will be more effective than a traditional mesothelin CAR-T therapy. • Laborious efforts to create HLA-1/2 null iNKTs for universal use is not supported by pre-clinical or experimental results and is conjecture at this point, although not incorrect. The investment in funds and time is questioned. • There is no clear rationale for how and why the applicant chose the ScFv CAR binder for this particular study. • Unlikely the T CAR constructs will work in iNKT. This is the major problem with this application. • Not clear why this program should be more effective compared to other T cell therapies. • The basis to use CB HSCs vs. other HSC sources is unclear, including use of hPSCs.
GWG Votes	Is the proposal well planned and designed?
Yes: 6	*none*
No: 7	• The applicant is completely focused on the iNKT platform. There is minimal to no significant work planned for optimizing the CAR construct for iNKT cells or for better understanding the disease biology of mesothelioma. • The proposal methodically described the studies that will lead to a candidate anti-mesothelin CAR iNKT cell. • Very thoughtful and laid out plan. • Well-positioned to draft a TPP and create a product. Transition to clinical applications to create a TPP have been proposed e.g. Tox, PK, PD, dosing, and human tumor efficacy testing using model systems. • Well designed and almost plug and play given a new CAR and generation of iNKTs are the simple requirement for application. • Unclear why and what evidence is creating the need to create HLA-E expression, HLA 1/2 null iNKTs and requirement for suicide switch (not required before for CAR-Ts).

	• Might be overly ambitious and not needed e.g. over engineered. A priority for early products should be provided if time does not support completion of work as proposed. • It appears that the entire proposal relates to feasibility. It is not clear what the discovery component of it is.
GWG Votes	Is the proposal feasible?
Yes: 8	• The proposal is feasible but lacks some a clear plan for understanding and elucidating some of the fundamental biology related to CAR constructs and mesothelioma biology. • Prioritization should be considered, as many cell types and engineering sets are proposed for various CB HSC derived MCAR-iNKTs. • The milestones and timeline are appropriate. • The team is qualified. • Highly qualified, including private sector partners that have worked together previously on similar projects, published, and been successful. • The appropriate resources are available. • The budget is appropriate.
No: 5	*none*

Application #	DISC2-12171
Title (as written by the applicant)	Spheroids of neural crest stem cells for neuromuscular regeneration
Research Objective (as written by the applicant)	The objective is to derive NCSCs from four human GMP iPSC lines (donor eligible), make them into spheroids, and determine the therapeutic effects of these cells in neuromuscular regeneration.
Impact (as written by the applicant)	Muscle denervation often leads to disability. A major hurdle of functional recovery is lacking reinnervation. We will use NCSCs to promote neuromuscular regeneration, and address this unmet need.
Major Proposed Activities (as written by the applicant)	• Derivation and characterization of NCSCs from iPSC lines • Fabrication and characterization of NCSC spheroids • Cell survival and neuromuscular functional recovery in immunosuppressive rat models • Optimization of the timing of cell transplantation • Demonstration of the efficacy of stem cell therapy in multiple NCSC lines
Statement of Benefit to California (as written by the applicant)	Muscle denervation often leads to muscle dysfunction and disability. A major hurdle of functional recovery is lacking reinnervation, and the types and sources of stem cells for effective neuromuscular regeneration remains to be identified. We propose to use NCSC spheroids derived from GMP iPSC lines (different sex, race and HLA type) to promote neuromuscular regeneration. This project addresses unmet medical needs and will benefit the diverse Californian population and our healthcare.
Funds Requested	$250,000
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 70

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

Mean	71
Median	70
Standard Deviation	4
Highest	80
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. Following the panel's discussion and scoring of the application, the scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 9	• Yes, the use of neural crest stem cells (NCSCs) for neuromuscular regeneration targets an unmet medical need. • Muscle atrophy and consequential disability due to the injury of peripheral nerve or spinal cord is relatively common and a failure of reinnervation and the reformation of neuromuscular junctions (NMJs) prevents functional recovery. Current treatment with the autologous nerve grafts leads to functional recovery in only 40 to 50 percent of patients.

	• Improving outcomes in these injuries is important.
No: 3	• Fresh new idea, but the candidate cell therapy may be problematic for their proposed application.
GWG Votes	Is the rationale sound?
Yes: 7	• Yes, using pluripotent cells as a source is based on compelling data. • The data on functional recovery is compelling. • NCSCs contribute to early muscle formation and maintenance of skeletal muscle progenitors are persist in low abundance in adult tissues. Human iPSCs provide an unlimited source for NCSC derivation and allow for allogenic cell transplantation. • Previous published work showed that transplantation of NCSCs into nerve conduits promotes nerve regeneration and functional recovery through both Schwann cell differentiation and neurotrophic signaling involving growth factors. • In Fig 2 applicant shows that NCSC spheroids drastically improved cell survival in vivo. Spheroidal culture can prevent anoikis-mediated death that occurs in 90% of transplanted single cell suspensions thus reducing the efficiency of cell transplants. • Applicant plans for a preclinical rabbit model, proposes to partner with the CROs for acquisition of GMP iPSC lines with donor eligibility, work on scaling and raise funds for additional investors.
No: 5	• The proposed experiments focus on the efficacy at one to two weeks post injury, but there are no supporting data that delayed transplants would be beneficial. • In addition, there seems to be no reason to jump from day zero to day seven without any intervening time point. • There is no comparison with uninjured animals, and thus we have no way of knowing how extensive the recovery is. It is better than saline, but if it is still a fraction of percent of normal, then how meaningful is it? • No data are presented on nerve regeneration. This is particularly critical in light of the absence of comparison with uninjured animals, and the question of whether the benefits seen are due to interactions with nerve cells are or just effects of the spheroids. It's also not clear whether the NMJs seen represent sprouting from non-injured nerve cells. • No data are presented on what the transplanted cells turn into. • Problem of allogeneic cell source is not discussed - that's a major issue.
GWG Votes	Is the proposal well planned and designed?
Yes: 7	• The spheroid strategy is a strength. • In Fig 3 they show that NCSC spheroids enhanced “functional recovery” and NMJ formation following denervation injury. No behavioral test but marker of nerve innervation are increased (this is not compared to single cell injections). • Proposal does not address how many cells are needed to achieve this amount of recovery and whether long term survival of the graft that mainly differentiates into Schwann cells is an advantage. • Injuries in human are highly variable and there is no discussion as to what kind of injury at what stage would qualify for a transplant - inclusion criteria? variable differentiation profiles? • The immune system plays an important role during injury. Both animal models are immune compromised, which could lead to a different environment than what is found in the presence of an immune response.
No: 5	• Yes, the experiments are constructed in a rigorous manner. However, critical controls in the animal experiments are missing. • The need to diagnose injuries is not considered. • The distances involved in muscle injections in human to the nerve injury are not considered. • Experiments have been done with injection of spheroids on the same day as the denervation injury, and it is not clear what this timeframe would correspond to in terms of suitability for clinical translation. It does seem rather rapid. • No information is provided in regards to immune rejection problems and how these will be overcome.
GWG Votes	Is the proposal feasible?
Yes: 11	• The milestones are ordered in a logical sequence. • Diagnosis is uncertain and surgeons usually wait up to 6 month before an intervention is considered thus timing of the transplant is not well defined. Would delayed transplantation work?

	• What is the spontaneous rate of functional recovery of this kind of injury? Is the window and severity suitable to see functional recovery and to allow for time line analysis? • The distance from muscle to nerve injury site means that the proposal as written is probably not feasible. • Strong team that is likely able to execute the proposed experiments.
No: 1	*none*

Application #	DISC2-12157
Title (as written by the applicant)	Molecular manual for human hematopoietic stem cell development
Research Objective (as written by the applicant)	Generate a map for human blood stem cell development that will be used as a manual to guide pluripotent stem cell differentiation in vitro to improve the treatment of blood disorders.
Impact (as written by the applicant)	This will improve the treatment of inherited and acquired blood and immune disorders by providing new sources of hematopoietic stem cells for transplantation
Major Proposed Activities (as written by the applicant)	• Perform single cell RNA sequencing on human blood forming tissues at different stages of development to establish a molecular manual for human hematopoietic stem cell development • Define the molecular identity of blood forming stem cells during human development and establish scorecards with markers specific of each stage of blood stem cell maturation • Identify the vascular precursor cells from where blood stem cells emerge and establish scorecards to mark specific stages of endothelial to hematopoietic transition • Use the molecular manual of blood stem cell development to identify signaling switches that direct blood stem cell specification from endothelium and their maturation to functional stem cells • Compare blood stem and progenitor cells generated in culture from pluripotent stem cell to the molecular scorecards and define the developmental stage that they represent. • Utilize the molecular manual for human blood stem cell development and our specific pluripotent cell reporter lines to guide the differentiation of blood stem cells in culture
Statement of Benefit to California (as written by the applicant)	This work will benefit the citizens of California by enabling the development of new sources of hematopoietic stem cells and other blood and immune cells for therapies. These findings may help overcome the limitation of HLA matched blood stem cells for ethnic minorities and individuals of mixed ethnic backgrounds. These findings will also help generate better culture models for hematological diseases such as sickle cell anemia, and understanding blood diseases that originate in utero.
Funds Requested	$250,000
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 69

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	69
Standard Deviation	6
Highest	75
Lowest	50
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 9	• Overcoming the barrier to creation of HSCs is important. Investing in basic research to better understand their biology should advance the field. • Potential to generate blood. • Has been a significant bottleneck. • Great science.
No: 4	• Very strong basic science proposal. • Will not achieve a therapeutic target ready for translation within the next few years. • The work is important but will not result in a candidate for an IND or a tool in one year.
GWG Votes	Is the rationale sound?
Yes: 11	• Basic science rationale is strong, having a better understanding of normal HSC development from the early embryo through to adult will likely be a useful tool. • Understanding basic biology of blood development seems a necessary step to move forward. • Good developmental biology • The science is great and could be a tool for others to use.
No: 2	• They claim that there is a "developmental hierarchy" as a basis for their work, but this ignores the possibility of transdifferentiation or developmental plasticity or network organization.
GWG Votes	Is the proposal well planned and designed?
Yes: 7	• Reasonable approach using human cells. • Gene expression patterns might be informative to generate better differentiation protocols. • Strong team but not enough personnel to accomplish the project in the time frame allocated. • The work should be more oriented towards translation.
No: 6	• Too many milestones, most with overlapping timelines where initiation of activities for one milestone are dependent on completion of a prior step, but the listed timelines do not incorporate that dependency. • Far too ambitious for time and funds allowed. • Overly ambitious. • They propose to create a comprehensive single cell transcriptome "map." But what is a map? Clearly not the intracellular location of transcripts within a cell. So if not that, then what? • "We hypothesize that knowing the molecular signature of human HSCs will facilitate their identification in all tissues and stages, spanning their emergence, migration, expansion and molecular maturation." This is not so much a hypothesis as an already well known fact. • "We hypothesize that placing [...] cells into this [...] hierarchy will indicate the molecular and cellular barriers to HSC differentiation, and [..] how these barriers may be overcome." This is vague but interesting. What would the alternative approaches be for determining the molecular barriers to HSC differentiation - perhaps some form of interpretable machine learning? If so, convince us that making a "map" is a better and more rigorous approach than machine learning. • What do you mean by "cellular barrier"? Perhaps milieu? If so, maybe use "milieu" instead, in order to be more precise. • How is a "scorecard" different from an "expression profile"? Does a scorecard have well designed statistical properties or is it just a pretty picture like what was shown in the proposal figure? • The proposal tended to focus on data visualization techniques and less on techniques with statistical rigor. It was unclear how visualization would be valuable in advancing this research, and yet it seemed to be a primary tool. • How will the multiple testing burden of the great many dimensionality techniques be overcome? • "Human PSC reporter lines for HSC regulators will monitor PSC differentiation to HSCs in real time."

	Arguments for the importance of these 5 genes, and perhaps even necessity, are included in the proposal, but not arguments for sufficiency.
GWG Votes	Is the proposal feasible?
Yes: 4	• The proposal is feasible but not in the listed time frame.
No: 9	• The project is far too ambitious. Several key personnel had only 1% to 5% effort for jobs that would require much more FTE than that. The timeline is not sufficient to achieve the aims. The budget is too small. • Developing user-friendly tools can be a very expensive proposition in the software development industry. I wonder if a major fraction of the budget is going to be spent on developing a user friendly tool if enough budget will be left over for the molecular data acquisition and analysis. • This is a very strong team. With enough time and resources, they could be very successful. • Previous work that was funded to do this kind of work has not been fruitful. • Long term goal that does not fulfill the urgency of the CIRM mandate. • Exceptionally ambitious. • Difficult to accomplish in one year, this work would better be suited for multi year basic research application. • This is basic science. Not translatable. • Too ambitious even to generate a tool in 1 year. • Too ambitious with an unachievable timeline.

Application #	DISC2-12135
Title (as written by the applicant)	Prevention of Neuromuscular Junction Loss in Amyotrophic Lateral Sclerosis
Research Objective (as written by the applicant)	We will develop SKNMJOs which enables efficient NMJ formation from ALS-hiPSCs to screen for small molecules that prevent NMJ loss in ALS.
Impact (as written by the applicant)	One of the earliest events in ALS is loss of neuromuscular junctions (NMJs) leading to eventual loss of muscle function. We will identify a small molecule candidate to prevent NMJ loss in ALS.
Major Proposed Activities (as written by the applicant)	• Develop SKNMJOs from patients with ALS including both familial and sporatic ALS-hiPSCs. • Develop high throughput screen using SKNMJOs • Perform secondary screens to verify and narrow down targets promoting NMJ function in ALS-hiPSCs • Evaluate 1-2 small molecule candidates for ability to support NMJs in animal models of ALS. • Develop Target Product Profile for small molecule preventing NMJ loss in ALS
Statement of Benefit to California (as written by the applicant)	Approximately 5,000 people in the U.S. are diagnosed with ALS each year and it certainly affects many CA patients and families. ALS patients have progressive weakness, wasting, and paralysis of muscles of the limbs and trunk, as well as loss of control of vital functions such as speech, swallowing, and eventually breathing. Prevention of progression of ALS will save lives and prevent associated health care costs and undue burden.
Funds Requested	$250,000
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 65

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

Mean	68
Median	65
Standard Deviation	9
Highest	85
Lowest	60
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	1
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 9	• The applicant provides strong preliminary and published data that supports the ability of generating relevant human organoid models. Importantly, their motor neuron-skeletal muscle co-culture system shows robust contraction and expression of mature muscles and myotubes and transmission capability. To overcome the detachment of the skeletal muscle culture during contraction, they generated a robust 3D system of skeletal neuromuscular junctions in organoids.

	• The inclusion of sporadic occurring ALS -hiPSCs is a strength as most research has been focused on the familial form, which is less common. • The project describes excellent screening technology for identifying candidate ALS therapeutics. Current therapy for this disorder is very limited and disease progression is highly disabling. • An extensive source of hiPSC lines that cover all ages, mutations, races, sex and genders of ALS patients has already been generated through CIRM funded stem cell core (over 350 ALS hiPSC samples). • This study is targeted to identify strategies that will prevent the loss and dysfunction of the neuromuscular junction. Thus, this strategy will have to be applied shortly after diagnosis. It should have been discussed how this will be achieved during the verification of the drug in the animal model and eventually in patients (i.e what markers of early disease onset will be used to identify the right timing of any potential drug). • This proposal would have been stronger as a Tools application. Whether a candidate therapeutic will emerge from the screening is not certain.
No: 4	• The technology to develop an organoid model of ALS is the strength of this proposal. However, the technology necessary to identify small molecules is lacking.
GWG Votes	Is the rationale sound?
Yes: 6	• Project is based on exciting new evidence implicating muscle and specifically the NMJ in early pathogenesis of ALS. These discoveries open up new avenues for intervention. • Both sporadic and hereditary ALS presents with neuromuscular junction dysfunction early in disease progression. • Aim 2 is based on the assumption that patient-derived organoids will show in vitro and junction loss and dysfunction. This has not been tested.
No: 7	• Seems essential first to demonstrate a reproducible ALS-specific phenotype in organoid-based NMJs from both cases with known mutations and sporadic cases. It does not seem safe to simply assume that this will be a viable "disease in a dish" model without data. • Preliminary data for the organoid modeling are solid. However, there is no preliminary data for small molecule development.
GWG Votes	Is the proposal well planned and designed?
Yes: 5	• The screening approach will be developed in collaboration with a key personnel, and while the LOS letter states that “Preliminary data ... already suggests that they will identify novel and interesting targets for subsequent studies,” the data are not provided in the application. • There is no animal model that would represent sporadic ALS, thus a lack of efficacy in the animal models might not predict a lack of efficiency of the drugs in humans.
No: 8	• The project may not yield a candidate, since progress beyond Aim 1 is crucially dependent on finding a robust hit in the screen. • The in vitro 3D differentiation system is outstanding as are provision for cellular phenotyping, functional assessment and screening approach. • The organoid modeling is well planned. • Proposal for in vivo assessment of potential hits is thorough and well considered with appropriate endpoints. • There is insufficient detail regarding the compound library to be screened, or the rationale for its use. There is no information on what the mechanistic basis for expecting compounds to reverse NMJ degeneration might be. No positive control compound, no timeframe for screen, no information on variability from well to well. • Application assumes a robust hit will emerge. It is not clear how this assumption is justified. Some preliminary data on positive controls for the screen would be really good. This would show the anticipated sensitivity and specificity of the methodology. • No information on how lead compound if one emerges might subsequently be optimized. • The small molecule modeling is missing.
GWG Votes	Is the proposal feasible?
Yes: 6	• Maybe- A major question is whether the organoids generated from the various patient populations will actually develop a phenotype in vitro that then can be "rescued". • Questions of variability are not well addressed • To determine efficacy they propose to measure the activity of human organoids. It is not clear how many motor neurons will be sampled and what results would confirm a pre-pathological SKNMJO. • The high throughput screens starts with organoids that are determined to be functional based on the presence of presynaptic vesicles. However, it could be that some of these

	patient-derived 3D cultures will not have functional NMJs as part of the pathology. These organoids would be lost from the analysis and the applicant would actually miss the most affected organoids.
No: 7	• Failure to achieve timely identification of a lead compound will delay Aim 2 indefinitely. • Not convinced the full work plan can be carried out in the time frame allowed without demonstration that the model reveals a phenotype that reflects the disease. • The PI is an outstanding stem cell biologist who has had great success in generating skeletal muscle from hPSC. PI is joined by a collaborator who is expert in screening and has developed innovative microfluidic technology for assessing muscle contractility. Great combination of expertise. • More information on compound libraries would be helpful, and potential collaborations with medicinal chemists would give more confidence that a therapy could develop out of the work.

Application #	DISC2-12107
Title (as written by the applicant)	Ameliorating drug-resistant human pancreatic cancer stem cells.
Research Objective (as written by the applicant)	We will develop DC-1 that kills drug-resistant human pancreatic cancer (PC) stem cells to halt tumor progression, metastasis, and drug resistance that targets extrinsic and intrinsic regulators of utility to treat PC.
Impact (as written by the applicant)	DC-1 will overcome long term efficacy and relapse shortcomings and drug resistance, providing treatment for all patients including underserved populations working against tumors with common mutations.
Major Proposed Activities (as written by the applicant)	• Produce 2-5 grams of DC-1 in >95% purity by NMR, LC and MS and potent in vitro. Amount based on calculations from previous in vivo studies and discussions with clinical collaborators. 1-3 months. • Conduct human patient-derived PC xenograft studies to test DC-1 to decrease tumor volume and weight. DC-1 potency against human patient-derived PC greater than vehicle and gemcitabine 3-4 months. • Conduct hPCSCs limiting dilution studies in mice to show efficacy and optimal dose regimen for future advanced xenograft studies. Show selectivity of DC-1 for ameliorating hPCSC cells. 3-4 months. • Prepare pre-IND summary. Send to the FDA. Data will be of predictive value and clinically relevant. A full IND is beyond the scope of this proposal; a pre-IND will support one. 2 months
Statement of Benefit to California (as written by the applicant)	In CA, >6,000 people are diagnosed every year with pancreatic cancer (PC). PC is increasing: PC is now the 3rd most common cause of mortality due to cancer. PC healthcare in CA costs >$1 bil annually. PC is more common in older adults but unfortunately, drugs to treat PC are ineffective and cause serious side effects. DC-1 will kill drug resistant PCSCs and address an unmet need because it is potent against tumors with all common mutations including those found in underserved populations.
Funds Requested	$249,389
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 62

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

Mean	61
Median	62
Standard Deviation	5
Highest	65
Lowest	50
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 4	• High unmet need.
No: 9	• There is an unmet need as pancreatic cancer is the most lethal major cancer in the US and there are no curative chemotherapeutics. • Currently, no drugs have shown clinical effects to patients with pancreatic cancer and/or effects on relapsed pancreatic cancers. As such the goal, if achieved, could have major impact the field. • The applicant presented thoughtful options for project progression. Highly detailed tables, procedures, and figures describing drug characterization and in vivo efficacy on orthotopically transplanted cells are presented. • The candidate is unlikely to succeed as a stand-alone drug. • This application describes drug development, not stem cell technology. • The stem cell basis of the technology is only relevant if cancer stem cells (CSCs) are being affected. This may or may not be the case, as selectivity to CSCs has not been demonstrated directly. • The project is highly advanced, and Aim 4 actually will develop pre-IND set up so intrinsically translational. This is a drug advancement proposal, but is premature in the absence of a target and mechanism of action.
GWG Votes	Is the rationale sound?
Yes: 3	• Standard scientific rationale for single drug development. • Strong preliminary data but limited to cell lines. Primary patient samples should be explored, with or without KRAS mutations, etc... • Drug tests in mice receiving orthotopically transplanted spheroids from well-characterized PC patients would be more robust. • Proposal claims a 60% inhibition in tumor volume (Fig 3) and elsewhere it is claimed that "DC-1 was effective at producing a decrease in tumor volume of 65% in an orthotopic model of PC tumor implantation". The experimental design indicates this should actually be considered as slowing further growth, not decreasing tumor volume. • hPCSCs are transplanted orthotopically into the pancreas and allowed to grow for 10 days before drug or vehicle treatment. 28 days later mice are sacrificed. No mention is made of assessing tumor volume at the start of treatment (day 11). Presumably, a 60% reduction in treated compared to vehicle still represents significant tumor growth despite treatment. • The drug is tested in a PC "stem cell" line, which is described as a highly validated human Pancreatic Cancer Stem Cell line showing aggressive growth, stem-like characteristics, and cancer drug resistance. • Although combinations are mentioned to be beyond the scope of this proposal, other chemotherapeutic agents, eg. Gemritabine, could be part of the resistance. • Target unknown. This is concerning. Unclear how pharmacodynamic information was determined? • Highly advanced, PK, PD, ADMET and in vivo testing done already. The use of DC-1 at nM levels is impressive. However, patient derived xenograft testing, and not a single cell line, is required. • Unclear this is targeting pancreatic CSCs, but CSC assays are used in development of DC-1. • Claims of modulating molecular pathways are unclear.
No: 10	• Premature conclusions: Not clear that drug affects cancer stem cells. • Target of drug is not known.
GWG Votes	Is the proposal well planned and designed?
Yes: 3	• The proposed experiments do not evaluate the capacity of the drug to shrink tumors. • The studies did not test, as claimed, whether the drug DC-1 i) reverses cancer stemness and ii) overcomes drug resistance in vivo. Testing the first objective would require analysis at time points early in drug response, not in tumors after 28 days of treatment. The second objective is vague – resistance to what drug(s)? No studies of drug resistant cells are described. It is simply presumed that the PC "stem cell" line is "drug resistant". • Major weaknesses in testing objectives are not addressed. The study does not test the claims made. • A huge amount of work is proposed but important questions are not appropriately addressed.
No:	• First two tasks are not related to cancer stem cells.

10	• Cell line used is not well defined. • Generation of pre-IND is clear and possible. Well designed, and very, very detailed. Clearly experts. Strong CRO used. • Figure 1 and 2 do not measure self-renewal or CSC selectivity. The claims are not supported. This would have to be done clonally, or with limiting dilution assays. The effects on CSCs is the same as bulk cells. No fold differences are seen or compared. So, DC-1 works on CSCs, but no data supports DC-1 preferentially targets CSCs.
GWG Votes	Is the proposal feasible?
Yes: 7	• Highly advanced project, models in place, along with production of DC-1 at the levels required. • The project objective, to develop DC-1 as a chemotherapy to target human Pancreatic Cancer Stem Cell or their extrinsic and intrinsic regulators and treat drug-resistant PC, is not fully tested. • The team is qualified. • Highly qualified team and divided to apply expertise to each step of the proposal. • Established and well published experts in each of their respective fields/area. • Facilities are excellent. • The budget is appropriate for the research proposed.
No: 6	*none*

Application #	DISC2-12106
Title (as written by the applicant)	A Controlled Release Biomaterial for Improved Survival, Innervation, and Functionality of DA Neuron Cell Replacement Therapy for Parkinson's Disease
Research Objective (as written by the applicant)	A combination cell+biomaterial therapy for Parkinson's disease.
Impact (as written by the applicant)	Clinical data for PD thus far has revealed that the survival of DA neurons after implantation remains extremely low (1-5%), and treatment benefits are only noticeable >10 mos. after implantation.
Major Proposed Activities (as written by the applicant)	• Synthesize / characterize biomaterial using design of experiments and identify optimal controlled release profile (Months 0-3). • Quantify in vitro potency of biomaterial on hESC-derived DA neurons using clinically meaningful performance metrics (Months 2-6). • Validate in vivo efficacy of DA neurons implanted with biomaterial in a rat model of PD benchmarking to DA neurons implanted in conventional buffer (Months 5-11). • Prepare first drafts of Target Product Profile (TPP) and FDA CBER INTERACT briefing documentation (Months 5-11).
Statement of Benefit to California (as written by the applicant)	In California, Parkinson's disease affects an estimated 60,000 adults, with correlations to individuals exposed to pesticides, such as those involved in CA's large agricultural industry. Cases are expected to increase 50% by 2030, amounting to a projected economic burden of more than $79B by 2037 in the U.S. This proposal to develop an effective combination cell + biomaterial therapy aims to alleviate this significant healthcare burden on Californians caused by PD.
Funds Requested	$248,840
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 60

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

Mean	62
Median	60
Standard Deviation	4
Highest	70
Lowest	55
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 6	• Parkinson's disease is a significant problem as a replacement therapy using human pluripotent stem cells provides an attractive therapeutic approach validated clinically.

	Thus the work proposed would add significant value. This application, if successful, would provide significant impact as it would help with neuronal survival. ● Biomaterial has proven beneficial effects. ● Approach not novel.
No: 8	● Transplantation of ES-derived dopaminergic neurons and fetal tissue in animal models of Parkinson's Disease and humans, respectively, has shown promise for alleviating PD symptoms but therapeutic benefits are delayed likely due to poor cell survival after transplantation. Therapies that promote survival of ES-derived dopaminergic neurons after transplantation could enhance and accelerate therapeutic efficacy of the procedure. ● This encapsulating system might help in increasing the successful outcome of the cell therapy based on transplanting human iPSC-derived DA neurons. However, it does not represent any stringent limitation for the clinical testing of this approach. ● The benefits of combining functionalized biomaterials with grafting neurons should be very clear and significant in order to favor the combination of the two approaches. Pure neuronal grafts are already well advanced in clinical trials and have shown strong therapeutic effects. Functionalized biomaterials might have as well some intrinsic downsides such as promoting inflammation and immune response. Thus a careful examination is required to understand the real advantages of this combination. ● Too preliminary to reach a candidate.
GWG Votes	Is the rationale sound?
Yes: 9	● In all likelihood yes because it improves transplantation performance and builds on well-established biomaterials that help cells to survive and integrate after transplantation. ● A solid body of evidence indicates that GDNF can sustain survival of grafted neuronal cells and promote their maturation in the transplanted brain tissue. Thus, GDNF is a good candidate for improving the successful potential of cell therapies for Parkinson's disease. ● Preliminary data showed that embedding grafted neuronal cells in the prior system sustained survival and integration of the receiving neurons in the host brain parenchyma. Applicants did not elaborate why the new formulation contains only one factor and not the other factors. On this point of view, the new controlled release system needs to be again fully evaluated for its capacity to achieve similar beneficial features.
No: 5	● Embedding ES-derived dopaminergic neurons in hydrogels have shown very promising results in promoting cell survival and alleviating symptoms in a PD rat model faster than comparable DA transplantation studies. ● Drug delivery with the proposed biomaterial is a well-established method for local or targeted sustained release of water soluble molecules. ● The hydrogel strategy is poorly described, and no reference is cited. ● The promise of the product was likely a combination of neurons embedding in the immunomodulatory/pro-regenerative gels and the effects of protein delivery. Lack of a control with non-gel-embedded cells co-injected with protein hydrogels does not allow one to conclude that the promising results observed were the result of just protein release. ● It is not clear why the team does not want to further test the prior hydrogel formulation given the promising results, and wants to explore a completely different approach. ● Proposed protein delivery with the proposed biomaterial is not a novel approach. ● The safety of implantation of the proposed biomaterial in the CNS has not been proven. It is possible they may damage the tissue and worsen host immune responses. ● Rationale of beneficial effect being due to the protein alone is premature.
GWG Votes	Is the proposal well planned and designed?
Yes: 5	● Well-discussed plan. ● Preliminary data are provided with a different biomaterial than what is proposed - no explanation is provided for the rationale of the switch. ● The proposed product will be scrutinized for controlled release and its effects on neurons in culture and after brain transplantation. In case all these objectives will be successfully accomplished, the system will be of interest for future pre-clinical development. However, a better in vivo characterization would substantially strengthen this proposal. ● The experimental plan is rigorous and logically developed. The release pattern will be scrupulously tested in the dish, but might be strongly altered after cell transplantation in the tissue. No experiments are directly addressing this important aspect. ● Some potential pitfalls are discussed with convincing alternatives. However, in vivo studies lack some important functional assessments. 1) Analysis of DA release in vivo by microdialysis and overall DA quantification in the tissue. 2) Functional readouts by FOS immunostaining after amphetamine challenge.

	• Too much of of the drug might have serious detrimental effects on maturation of grafted neurons. Actually, embedded neurons might be exposed to high drug concentrations for an extensive period. Detailed analysis of axonal targeting of the grafted neurons within the host tissue will provide answer to this hypothetical downside.
No: 9	• Clear and detailed description of rationale, experimental approach (tasks), statistical consideration, justification of chosen models, anticipated results and potential pitfalls/alternative strategies for each milestone. • Timeline for completing the milestones is appropriate. • Network of consultants with relevant expertise has been generated that will help address any pitfall and will help the study progress. • 2D culture of neurons in laminin-coated wells does not represent the in vivo 3D condition after transplantation. • Delivery of ES-derived dopaminergic neurons without a hydrogel vehicle may decrease their viability as mentioned (excessive shear forces). • Generally good, but significant biomaterial questions.
GWG Votes	Is the proposal feasible?
Yes: 8	• Robust preliminary data supports the notion that the embedding and grafted neuronal cells described with the prior biomaterial and protein system promote survival and integration. Data with the proposed biomaterial, even preliminary, is not presented. • In general yes, but no experience provided with the new material.
No: 6	• Milestones are clearly described and will generate meaningful data within the expected timeline. • Without preliminary data for safety and efficacy of co-implantation of protein-delivering biomaterial with ES-derived dopaminergic neurons in the brain, in vivo experiments may not show improvements and could potentially worsen the outcome previously observed for prior hydrogels. • The milestones are nicely organized in a logical development from in vitro to in vivo testing. However, the first part regarding the validation of the biomaterial and its dependent controlled release of the drug is yet to be undertaken with no preliminary results presented. Thus, the validation of the system for controlled release might take significant more time than the one planned in the project. • Excellent team, who has developed the method for implantation of ES-derived dopaminergic neurons in prior hydrogels and external consultants for each task proposed to complete the milestones. • The team gathers a group of experts with high complementary expertise covering all the disciplines and technologies relevant for this study. • Excellent applicant environment having access to basic laboratory equipment and subcontracting the animal studies to known CRO. • Appropriate budget with personnel effort proportional to expected contribution for each milestone task. • The budget is fully justified by the experimental program, the workload and the personnel involved.

Application #	DISC2-12141
Title (as written by the applicant)	Assessment of Novel Depots of Adipose-Derived Stem Cells for Chronic Rotator Cuff Injury
Research Objective (as written by the applicant)	To show that fat-derived stem cells collected from around our muscles is a safe cell source for repairing chronic rotator cuff injuries that is better at regeneration than other common fat sources.
Impact (as written by the applicant)	Develop an adult stem cell-based intervention to be used in concert with surgical repair that will encourage muscle regeneration and prevent re-tearing of the rotator cuff.
Major Proposed Activities (as written by the applicant)	• Establish the degree of improved regenerative potential of stem cells derived from fat surround the rotator cuff muscles compared to abdominal fat. • Establish why fat from around our muscles is better at regeneration by assessing immune response, tracking stem cell location, and correlating position and amounts with tests of muscle function.
Statement of Benefit to California (as written by the applicant)	More than a half million Californians live with chronic rotator cuff tears. While there have been improvements in surgical repair methods, re-tear rates are as high as 50% in the decade following surgery. Degeneration of cuff muscles limit the success of surgical repair, so here we will use fat from around rotator cuff muscles to develop an injectable cell population that regenerates muscle in conjunction with surgical repair, thus increasing patient quality of life.
Funds Requested	$250,000
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 60

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

Mean	62
Median	60
Standard Deviation	6
Highest	75
Lowest	50
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 6	• The concept of using the proposed cells to engraft into rotator cuff muscle is a good one though the evidence for these cells acting through that mechanism is not yet strong. • Cells could work but outcome will not be known until the project is completed. • Impact is based on patient data that was generated in 1991; updated information is needed. • Yes, the product could induce a regenerative muscle response and outcomes in older individuals with rotator cuff injuries.

No: 8	• The proposal on use of the stem cells to treat rotator cuff injuries is not much improved over prior two submissions that were not deemed sufficiently meritorious to recommend funding. • Unlikely that a change in cell source will be transformative to meet the need. • Not clear that sufficient cells can be obtained routinely from epimuscular fat of elderly humans, without expansion.
GWG Votes	Is the rationale sound?
Yes: 3	• Clear indication of the end-product is provided.
No: 11	• The basic rationale is sound, but to be competitive with existing cell therapy approaches for rotator cuff, the mechanism would need to be proven as engraftment and differentiation rather than trophic repair and this is not certain. • Unclear that the major contribution of the cells would be action as stem cells to build muscle - more likely trophic as for most applications of MSCs, as generally found in >1000 clinical trials of such populations, very few of which have led to major clinical benefits or even publications. • Preliminary data remain unconvincing. • The notion that the cell population is functioning primarily as stem/progenitor cells in the clinical application, rather than as a transient source of potentially useful trophic factors, is not well supported. It is also not unlikely that culturing MSCs from more readily available sources under appropriate conditions would be able to reproducibly generate cells with comparable properties. • The mechanism of action and preliminary data are not strong enough to support the proposal.
GWG Votes	Is the proposal well planned and designed?
Yes: 4	• The project is well designed but ambitious for the time-frame available. • Okay, but the third submission of this application does not seem to have very much improved. • Variability of donor population is not well discussed.
No: 10	• Plan could probably generate a candidate that would be acceptable for an IND. Translation to a transformative product, however, seems unlikely. • Planning does not indicate how to generate a highly consistent product from many individual humans of different ages and physiological states. Extrapolating from the model to medical practice seems a major pitfall not dealt with well in the application. • Milestone 2 seems based on the premise that the major activity of cells would be as direct muscle stem/progenitors. The principle activity of the proposed cells seems more likely to be as transient sources of trophic factors. • The regulatory path seems improper. • The dosing does not seem reasonable given the yield from the cell harvest.
GWG Votes	Is the proposal feasible?
Yes: 7	• Overall the project is feasible but it is not completely clear how the full data set will be evaluated given the multiple end points. • As noted, reasonably straightforward to get to an IND.
No: 7	• Not clear, cell numbers that provide a therapeutic dose might not be achievable.

Application #	DISC2-12144
Title (as written by the applicant)	Differentiation of Vd1 gd T Cell-derived Pluripotent Cells for Use in Solid Tumor Cell Therapy
Research Objective (as written by the applicant)	The objective of this proposal is to differentiate induced pluripotent stem cells into broad targeting gamma delta T cells for cellular therapy to treat solid cancers
Impact (as written by the applicant)	Gamma delta T cells are potent antitumor cells but rare, and using iPS techniques to expand and differentiate these cells would facilitate their use to combat hard-to-treat solid cancers
Major Proposed Activities (as written by the applicant)	• Generate iPS lines for evaluation of differentiation protocols • Optimize differentiation of gamma delta T cells and conditioning
Statement of Benefit to California (as written by the applicant)	This proposed research will benefit the State of California in several ways. First, as the largest state, California has the most reported cases of cancer and deaths from cancer, and thus this broad targeting therapy against solid cancers, particularly cancers with traditionally low survival rates, would have a great benefit to Californians. Additionally, this work will all be conducted in California, thus contributing to the economy by way of sales to support our research and development.
Funds Requested	$250,000
GWG Recommendation	(1-84): Not recommended for funding

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	3
Highest	60
Lowest	50
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 7	• There is a need for novel cellular immunotherapies for solid tumors. • The work has the potential to generate treatments for solid tumors.
No: 6	• This project is based on stem cell reprogramming and cell fate instruction to create a cell product that is difficult to obtain from somatic sources and provides a patient specific allogenic source with potentially reduced GVHD concerns. • A strength of the proposal is it addresses a clear medical need. Immunotherapy is currently of limited use to treat solid tumors but long-term survival of rare patients with aggressive cancers is associated with active T cells in the solid tumor.

	• If successful, the approach of using Vd1 progenitor cells could greatly increase the utility of immunotherapy for solid tumors. • The proposed technology is not likely to result in a therapeutic. There is a paucity of preliminary data necessary to be convinced these Vd1 cells would be efficacious. • The application needs to test reprogrammed Vd1 cells against solid tumors in vivo before considering translational studies in phase 1 clinical trials.
GWG Votes	Is the rationale sound?
Yes: 2	*none*
No: 11	• Vd1 are touted to be superior to conventional T cells as candidates for solid tumor cell therapy for three reasons; 1) they target a wide variety of solid tumors; 2) they home more efficiently to solid tumors than do conventional T cells; 3) they do not generate graft-versus host reactions. • A significant advantage is that Vd1 cells are allogeneic, allowing the development of cells capable of treating solid tumors in a wide variety of patients. • The rationale is sound, given iPSC have been generated from T cells previously, as well as the ability to differentiate T cells. Attention to mouse vs. human, and age of literature is a concern, as many of the referenced papers that provide rationale have yet to come to fruition, eg. several papers referenced are not robust and have been abandoned. • The rationale is not sound. The role of gd T cells in solid tumors remains a matter of debate. There is biomarker and correlative data tha suggest a role for gd T cells, but no real definitive evidence that these cells are important for solid tumors. • Vd1 cells can be expanded in culture. No preliminary data to test their ability to shrink solid tumors. • The major concern is the preliminary data. Only one clone, colony, was generated at a very low frequency using V1 T cells. Even that clone was not fully characterized in a manner that would garner confidence. Eg. no teratoma assays, or growth kinetics shown. This, plus need to isolate original cell population for iPSC reprogramming suggest that Aim 1 will be much more difficult than anticipated, and may consume the majority of the grant resources. • Differentiation in xeno-free conditions for T-cells is not fully acknowledged to be very difficult and a single alternative method has been proposed. This is unclear, and no preliminary data of benefit or other xeno-free solution is provided. • The preliminary data is not strong enough to fully support the rationale. • Supportive data are scant. • In the absence of a target there might not be an effective response.
GWG Votes	Is the proposal well planned and designed?
Yes: 1	*none*
No: 12	• This is the first report of successful reprogramming of Vd1 to Vd1 T-iPSC. Many potential pitfalls are noted and discussed with alternative approaches to advance the program but the main goal is not addressed. • The applicants ignore basic aspects related to the biology of gd T cells and show no evidence for why their cell therapy will have an advantage in solid tumors. • The major weakness in the application is that is does not test the function of reprogrammed Vd1 cells in solid tumors. • The goals of the project should be directly tested at every opportunity, with convincing positive and negative controls. • The timeline appears to be rushed. The yield of the two Vd1 T-iPSC lines does not appear to be robust – how good are these cells? Perhaps there is not much confidence in the product at hand, thus the rationale for in vivo tests against K562 cells, not solid tumors. • The timelines to optimize and test methods for T-iPSC generation are not clear and no real mitigating plans have been provided. The primary data, and literature suggests Aim 1 will be very difficult, and the basis or benefit to use V1 T cells as cell origin for iPSC generation is not well supported vs. other iPSC lines. The number of lines required for this or application use is not acknowledged in the proposal. • The reprogramming strategy is too inefficient. • Why K562 cells are being used is not provided, given the aim is for solid tumors. What are the positive and negative controls here? Upper or lower thresholds of expected beneficial response that suggest these T-cells will be superior to other T cells or approaches?

	• It is unclear how PDX models will quantitate T- cell infiltration. Why are T-cells not delivered by IV? The homing and lack of GVHD and variety of tumors that V1 T cells can target were rationalized as the benefit, but not measured or explored in Aim 4. • Functional assays for immunologic responses are not clear. • Very few potential pitfalls are acknowledged, and this is concerning given the literature or lack thereof for xeno-free T cell differentiation methods and the experience of the applicants. • Limitations in PDX models to look at GVHD and cytokine incompatibility were not recognized or discussed. • Can V1 T cells generated by T-iPSC be compared to bonafide V1 T cells from humans? Are there data based on in-silico analysis? This would provide a surrogate measure to determine if these iPSC derived T cells are related to T cells in the human.
GWG Votes	Is the proposal feasible?
Yes: 5	• Weaknesses in the application are the yield of reprogrammed Vd1 cells appears to be poor and the major rationale of the application, to treat solid tumors, is not tested. • The proposed team is appropriately qualified and staffed. • Facilities at the institution are state of the art. • The budget is appropriate for the research proposed.
No: 8	• The applicants make broad claims related to the utility of gd T cells in solid tumors but their proposed studies don't actually address some of the fundamental aspects that are necessary for efficient translation into the clinic. • The preliminary data does not inspire confidence in these proposed assays and experiments. • Aim 1 is the major weakness for time limitations. • All the expertise and infrastructure is in place.

Application #	DISC2-12184
Title (as written by the applicant)	Engineered injectable pre-vascularized implant for neural stem cell transplantation after stroke
Research Objective (as written by the applicant)	The proposed research aims at developing neural implants that contain a pre-assembled vascular network within a hydrogel to help enhance the graft survival and integration with the host tissue.
Impact (as written by the applicant)	If successful, this research will enable a longer survival of the transplant and a better integration in the stroke brain, but will also enable a better control over these cells differentiation.
Major Proposed Activities (as written by the applicant)	• Biofabrication of microbead hydrogels • Biofabrication of VEGF nanoparticles • Neuro-vascular 3D co-culture in hydrogels • Stroke induction and brain delivery of NPC-laden pre-vascularized hydrogels • Assessment of behavioral deficit • Evaluation of graft survival and tissue repair
Statement of Benefit to California (as written by the applicant)	In California, the disparity between socio-economical statuses and ethnicity is evident: 3.2% of the white population is affected vs 4.6% of the black population. Similarly, 2% of college grads are affected while 4.1% of high school grads are affected. The household income also follows this trend with 1.7% of stroke patients earning above $75,000 vs 10% for those earning less than $50,000. This research would benefit a large population of low income and underserved communities in California.
Funds Requested	$250,000
GWG Recommendation	(1-84): Not recommended for funding

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	13
Highest	75
Lowest	30
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 6	• Stroke is the leading cause of disability in the US; Stem cell transplantation after stroke has shown promise in enhancing brain repair in pre-clinical models but not in humans likely due to poor survival and differentiation after transplantation. • Injectable biomaterials that can deliver and support neural stem cells while promoting revascularization could increase stem cell survival and promote regeneration after stroke. • Unmet need is high.

	• The proposed technology will utilize a successful strategy to promote revascularization in the stroke lesion. • The proposal does not provide progress from the previous study. • If successful, this could have a major impact. • Both neural stem cells and HUVECs will be allogeneic to the recipient and will require immunosuppression to prevent rejection. • Plan for translation is missing.
No: 7	• There is low likelihood that the pre-vascularized implant technology will lead to significantly impact an unmet medical need based on the previous failure of a similar technology by the same investigators and lack of solid publications, as well as a lack of clear difference between this technology and the failed one. The PI needs to strive in supporting this proposal with solid relevant publications and preliminary data. We are requested to evaluate a "failed study" previously funded by CIRM.
GWG Votes	Is the rationale sound?
Yes: 5	*none*
No: 8	• Strong preliminary data for feasibility of cell delivery through hydrogels, beads for reducing scarring and promoting cell infiltration; particles for promoting revascularization. • There is no preliminary data to support the hypothesis that combination of the three strategies would be beneficial. • Until the PI acknowledges what is unique in this proposal, specifically the technology being advanced here over what was previously funded by CIRM, the scientific rationale is weak to proceed with this hydrogel development proposal similar to the original study. • Without comparisons of the original technology and the present one demonstrating preliminary data that indeed graft survival and function are enhanced in the latter, then there is no preliminary data supporting that the proposed technology is an improvement over the previously examined and failed hydrogel. • There are some data to suggest that human/stem progenitor cells grow and differentiate using these hydrogels, but again the main theses here include enhanced graft survival and functional recovery following the pre-vascularized implant - without this set of data, the uniqueness of this technology over the previous hydrogel implant is not apparent. • No preliminary data. • Technology has some merit. • The design is too complex with HUVECs and the microparticles.
GWG Votes	Is the proposal well planned and designed?
Yes: 3	*none*
No: 10	• Strong preliminary data show three technological platform are available and combination may be beneficial. • Rationale for combining cell delivery through HA hydrogels and particles is strong but beads and HUVECs may not be beneficial. • There is low likelihood that this will amount to a high quality project based on the mediocre publication record of the PI (one paper each year for the past 3 years) on this seemingly claimed state-of-the-art implant technology. • No significant progress from a previously failed approach. • Side by side comparison is missing. • Inclusion of HUVECs is not justified and feasibility is not demonstrated • Too complex. Should start without the HUVEC cells. • No potential pitfalls outlined. • Not a single pitfall was discussed here. This is truly troubling as it appears that the caveats that led to the failure of the previous funded study were not even acknowledged and considered here. • The pitfalls are not well considered. • Potential pitfalls and alternative strategies are missing. • Track changes are still shown and several typos are present.
GWG Votes	Is the proposal feasible?
Yes: 5	• Unlikely to lead to an advanced approach. • The PI would likely build a strong team to execute these experiments.
No: 8	• With the failure of the previous study and without carefully taking to heart what was learned from the original study, presenting to the reviewers, and really providing approaches on how the PI will now navigate the pitfalls and problems originally

	encountered into the present proposal, there is just no way to evaluate the feasibility and logical transition from the previous to the present study. With 6 milestones, the timeline is overly aggressive and likely not to be completed here. ● The main flaw is excessive complexity. ● More details in task and success criteria would be desirable (only 2 out of 4 pages used). ● Very ambitious plan to combine three promising technologies and test them in vivo in a mouse model of stroke. ● The publication productivity of the PI is low. Clearly there is expertise in the assembled team, but this expertise needs to be translated into something concrete: solid paper and solid preliminary data supporting the proposal. ● PI has pioneered the development of therapeutic hydrogel biomaterials and drug delivery systems for brain tissue revascularization and regeneration and that resulted in three patents during their PhD and postdoctoral training. ● PI is a very junior investigator that could benefit from collaboration with an established investigator. ● Budget appears appropriate, but milestones definitely need to be reduced. ● Underbudgeted for the number of approaches proposed.

Application #	DISC2-12102
Title (as written by the applicant)	Treatment of Abdominal Aortic Aneurysm Using Scaffold-Based Delivery of iPSC-derived Smooth Muscle Progenitor Cells
Research Objective (as written by the applicant)	To develop human induced pluripotent stem cell-derived smooth muscle progenitors (iPSC-SMPs) as a therapy for treatment of abdominal aortic aneurysm (AAA).
Impact (as written by the applicant)	Currently, there are no pharmacologic therapies for AAA. If successful, delivery of autologous iPSC-SMPs to the site of AAA will halt or reverse the progression towards a rupture-prone aneurysm.
Major Proposed Activities (as written by the applicant)	• Optimizing iPSC-SMP dosing within collagen scaffolds for maximal therapeutic efficacy in a mouse model of AAA. • Assessment of iPSC-SMP biodistribution in the body. • Determining the mechanism of action of iPSC-SMP-seeded scaffold delivery. • Determining the safety of iPSC-SMPs in vivo. • Identifying the therapeutic candidate and generating the Target Product Profile.
Statement of Benefit to California (as written by the applicant)	We propose to generate human iPSC-SMPs for treatment of abdominal aortic aneurysm (AAA). Currently there are no pharmacological treatments for AAA. This stem cell-based therapy will benefit California by providing a new treatment for AAA. Production of cell-seeded scaffolds 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 AAA
Funds Requested	$250,000
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: --

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

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

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 2	• Abdominal Aortic Aneurysms represent a significant health care need. The current treatment options are limited to surgical interventions and stenting. • The proposed study utilizes stem cells as a patch. It is not clear that given all the current treatment options, the direct application of a path is a substantial novel improvement.

	• The observation that the potential beneficial effects are mediated through mediators secreted by the proposed cells is noteworthy and might offer a better approach. • There are concerns that the proposed method will be potentially very invasive and other methods might be more beneficial or have a higher likelihood to be translated to clinical applications.
No: 12	• Important disease and relatively widespread. • AAA can be quickly fatal and difficult to detect. • Translational potential for the technology is a concern. Autologous therapies are complex and expensive, and it isn't clear that the potential advantage of a cellularized scaffold balances those drawbacks. • This project is still at a very early stage. It is hard to assess whether this candidate will lead to the development of a stem cell therapy that will improve patient care but there is potential. • Immune suppression would be needed - not discussed by the applicant. • Some good science, but sounds like this is seriously flawed as a feasible and practical solution to the unmet medical need. • The application for an aneurysm involves surgery and would not work for an autologous therapy.
GWG Votes	Is the rationale sound?
Yes: 4	• The rationale is sound. • Rationale is not clear - is the focus on the secretome because cell replacement is not sufficient? • Approach would need significant surgery - therapeutic feasibility not compelling.
No: 10	• Preliminary data demonstrate an effect of iPSC-SMP conditioned medium so it isn't clear why a cell therapy is needed. • There is a major concern that the overall approach will not be feasible in humans. The application of the patch will require abdominal surgery, which will be the standard approach. There is no apparent advantage. • The mechanism is not clear and the therapeutic application is poorly chosen.
GWG Votes	Is the proposal well planned and designed?
Yes: 5	• Cell characterization is strong. The delivery scaffold is innovative. Tracking of cell fates is a strength. • Nice biomaterial approach. • The differentiation and scaffold strategy are strong. • Assessment of mechanism of action in Aim 2 is underdeveloped. • No statistical analyses in preliminary data. • Characterization of factors not proposed.
No: 9	• The overall study design is well presented and justified. • There are concerns whether the proposed approach is truly a substantial improvement to current treatment (i.e. open repair). • The most likely mode of action is due to paracrine effects. While this is discussed, one could conceptualize other treatment approaches. • Regarding the paracrine effects, the proposal does not aim to elucidate or further characterize underlying mechanisms. Therefore it is very descriptive and doesn't provide important and critical mechanistic insights. • The study design lacks a clear justification of the number of animals, a power analysis and a more detailed description of an integrated analysis plan. • I consider this early stage project underdeveloped to meet the expected outcome of the program announcement.
GWG Votes	Is the proposal feasible?
Yes: 8	• The project is a logical extension of prior work by this outstanding team in generating the cell population and delivery scaffold. • The milestones and timelines appear appropriate. • Technically sound. • The team is qualified to conduct the proposed experiments. • The team seems competent with a good track record. • The resources and infrastructure is appropriate. The budget appears appropriate.
No: 6	*none*

Application #	DISC2-12113
Title (as written by the applicant)	Skeletal stem cells for the treatment of Osteoporosis
Research Objective (as written by the applicant)	This proposal positions human skeletal stem/progenitor cells as a therapy for osteoporosis, based on preliminary data showing that these cells migrate to and repair bone.
Impact (as written by the applicant)	Skeletal stem cells (SSCs) offer a potential superior treatment for osteoporosis compared to current therapies, restoring bone integrity with minimal side effects and at a lower cost.
Major Proposed Activities (as written by the applicant)	• Optimize expansion of SSCs ex vivo • Determine alloreactivity of SSCs in vitro • Characterize homing, engraftment potential, and cell fate of SSCs • Confirm efficacy of SSCs to restore bone loss in a murine model of osteoporosis
Statement of Benefit to California (as written by the applicant)	Osteoporosis is a common disease that leads to fractures, even after low-energy trauma. As the aging segment in California increases, the prevalence of osteoporosis is also projected to grow. Current treatments mostly focus on stopping bone deterioration, but minimally help to promote new bone formation. Since the fundamental problem is that the cells capable of replenishing bone decline with age, we propose a novel therapy by transplanting "skeletal stem cells" to restore bone integrity.
Funds Requested	$240,628
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: --

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

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

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 3	• There is an unmet medical need for novel therapies that promote bone development and regeneration for osteoporosis. • Overall interesting idea with potential.
No: 12	• The proposed therapy based on the infusion of expanded adult human skeletal stem cells (SSCs) as an allogeneic product does not seem likely to result in a therapeutic candidate within the time frame and scope of the proposed project. The likelihood of achieving several key steps appears low, and few alternative options are presented.

	• The proposed work is comprehensive and mostly logical but depends on many different strands of research proving to be successful and there is thus a high risk of failure, reflecting the early stage of research using these recently described cells. • There is potential for impact as a defined population of skeletal stem cells would be an appropriate cell source to treat Osteoporosis. However I am not convinced that the proposed putative population of skeletal muscle stem cells is the appropriate target cell population. • Pharmacological approaches to treatment of osteoporosis focused on stimulation of osteoblasts have advanced significantly. These include use of parathyroid hormone-like factors, monoclonal antibodies that activate the Wnt pathway (e.g., through blocking a Wnt inhibitor), etc. The proposal does not provide compelling reason to expect that cell therapy with the contemplated candidate would be significantly more efficacious than therapies already approved or in advanced development. • Seems quite likely that allogeneic "off the shelf" product would be immunogenic. A prophylactic therapy to prevent bone fractures due to osteoporosis that would require immunosuppression seems problematic. • The improper rationale lowers the potential for impact.
GWG Votes	Is the rationale sound?
Yes: 2	• The basic rationale is sound. However the pathway from discovery science to translation is not well thought through and not logical and this weakens the proposal, especially because of the weakness of milestone 1.
No: 13	• The rationale that skeletal muscle stem cells may provide more effective results than mesenchymal stem cells is sound (as long identified cells are truly bona fide skeletal muscle stem cells). • The notion of using therapy with authentic skeletal stem cells to regenerate bone is sound in principle. However, the concept that the loss of SSCs is fundamental to osteoporosis and that infusion of fresh stem cells would ameliorate the disorder is not proven. For example, a deficiency in the bone microenvironment could be a fundamental problem that would preclude efficient engraftment or bone-building activity of the infused cells. • The PI provides some compelling preliminary data as following transplantation of these putative skeletal stem cells, donor-derived cells are detected, along with staining for Calcein, which shows mineralization. However, the therapeutic potential would be more convincing if there were pilot data showing co-localization of cells with human-specific antibodies for bone markers. • The premise behind Aim 1 is odd. Based on a FACS plot (Fig. 5), the applicant suggests that SSCs are more abundant when isolated the day after surgery instead of immediately (one wonders if staining to label all cells was performed prior to FACS to exclude dead cells). Based on this result, studies in milestone 1 are focused on quantifying SSCs over time (0, 1, 2, and 3 days) and identifying the proteins that account for this "ex vivo" expansion. • Data on increased number of candidate SSCs after further incubation of RIA effluent is interpreted as showing 3 rounds of division of these cells in 24 hrs. No direct evidence presented to support such rapid expansion of the cell population (e.g., testing for newly synthesized DNA in cells after the incubation period), and other possibilities seem more likely - release of cells from particles in effluent, changes of surface expression by some cells during incubation period, etc. • Weak rational as there is no discussion as to whether the cell populations will be viable. • Milestone 1 appears flawed. • Evidence that the candidate population actually represents SSCs is not convincing. Their relationship to recently described human SSCs and to "classical" MSCs needs further elucidation. • Preliminary data on biology of the cell population identified by the applicant has some positive features but are insufficient to compel acceptance that these are authentic SSCs. Need much more complete data on self-renewal potential and differentiation potential. • The fundamental problem in the disease may not be linked directly to the stem cell. • The allogeneic approach is questionable.
GWG Votes	Is the proposal well planned and designed?
Yes: 3	• Overall ok but over ambitious.
No: 12	• The project is planned more as a basic research project with the hope of a translational outcome but it is very unlikely that the work will provide solutions needed to the various technical questions.

	• One year of work for this project is not sufficient to justify translational work. They are at very early stages (working hypothesis). This project may provide some proof-of-concept but more solid demonstration will be necessary to justify moving into the clinics. • Milestone 1, collection of cells from bone and expansion is very weak. The increased cell number recovered after 24h incubation is more likely to be from cells migrating out of the bone pieces than proliferation. No evidence for proliferation has been provided, only for increased cell number. • It is really ambitious for a one year grant. • Plan for each Milestone has significant weaknesses. Overall the program appears overly ambitious and unlikely to be achieved within the proposed 12 month timeline. • The improper rationale leads to a poor research plan.
GWG Votes	Is the proposal feasible?
Yes: 3	• Maintenance of proliferation is not clear and might be a severe obstacle. • The goals seem appropriate.
No: 12	• The weakness of milestone 1 makes the entire project unfeasible. • It's an interesting project but is early stage and not feasible for a 1 year grant. • It is not feasible for the timeline of 1 year. Overambitious. • Too ambitious given the one year limit and the enormous work load. • Development of defined conditions to expand progenitor or stem cell populations is often extremely challenging & time consuming. The notion that this will be achieved as proposed seems wildly optimistic and based on a dubious premise. • Proposed immunological studies are just the tip of the iceberg of what would be required to determine the extent of the allo-transplantation barrier to the SSCs and, as likely would be necessary, development of an effective regimen to overcome it. No clear plan is presented for how such a regimen would be developed. The major problem of "off the shelf" cell therapy and potential scenarios that might be acceptable for the desired product are not addressed adequately. • Demonstration of some disease modifying activity (Milestone 4) may be achievable, although preliminary data on this point were not statistically significant nor even very encouraging, but determination of an "optimal dose to reach maximum recovery of bone mineral density" does not seem a realistic outcome of the proposed experiments. • Overall, reaching all four milestones in one year with the requested level of funding would be extraordinary - the proposal appears greatly overambitious. • Team reports that it has been working on these cells since 2016 without having published any data. Does not support level of productivity that would be required to achieve the ambitious plan. • PI's biosketch does not provide sufficient support for statement that the lab has a strong translational focus with regulatory / manufacturing / preclinical development expertise. One team member clearly has such expertise, but the proposal does not make clear what their specific contributions will be. Overall staffing doesn't seem enough to support the ambitious plan.

Application #	DISC2-12103
Title (as written by the applicant)	Small molecule neurotherapy for genetic Complex 1 disorders in children
Research Objective (as written by the applicant)	We will use patient-specific stem cell-derived neural cell lines to test our small molecule therapies in neural cells.
Impact (as written by the applicant)	To date, there are no targeted therapies for most mitochondrial disorders. As children suffering from these diseases have significant morbidity and mortality, this approach may have a huge impact.
Major Proposed Activities (as written by the applicant)	• Purification and expansion of iPSC-derived neural cells. • Optimization of assays for neural cells. • Compare normoxia and hypoxia in neural cells. • Examine PHD2 inhibitors in neural cells. • Examine the effects of inhibitors on phenotype and differentiation. • Perform bioinformatics of transcriptomic and metabolomic data.
Statement of Benefit to California (as written by the applicant)	Mortality and morbidity in children with mitochondrial diseases are not only devastating to the child and the family but also place a huge burden on the California health care system. If our therapeutic approach is successful, not only will children and their families in the grip of these diseases prosper but the burden on California will decrease.
Funds Requested	$249,863
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: --

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

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

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 6	• Mitochondrial diseases represent a complex spectrum of diseases with limited therapeutic options. While rare and although there is a broad spectrum of clinical presentations, in many cases, the disease is severe and often fatal at an early age. • Identifying novel treatment options is of great clinical need. • Important unmet medical need. • Approach not very novel.
No: 8	• Complex I disorders are important mitochondrial diseases for which no therapies exist. • The work seems incremental over what has been done before.

	• This proposal aims at testing PHD2 small molecule inhibitors to reactivate the hypoxia pathway with the rationale that this might be beneficial for Leigh's disease caused by dysfunctions in mitochondrial respiratory complex 1. The rationale has some weaknesses not properly discussed in the application and the experiments are exclusively on cell models leaving uncertain their predictive value in vivo and for clinical development. • It is a very early study which can not have substantial implications for any translational approach.
GWG Votes	Is the rationale sound?
Yes: 4	• Understanding this particular disease is valuable. • Using patient specific iPSC cell lines and the proposed differentiation in neural cells is sound. • There is supportive preliminary data. Cells for the differentiation appear to be collected. Protocols are developed and there is experience with the proposed methods. • The applicants state that a number of tasks will be performed before the funding of this application will start. It would be certainly beneficial if more aspects of the proposed work were established. • The rationale for the proposed drugs is established. The impact of hypoxia on the disease process is an important part of the preliminary data and supports the approach.
No: 10	• Main effect underlying the rescue of neurological effects in mice has been shown to not have been due to hypoxia. • The project is based on previous findings from another lab that described how the hypoxic condition can ameliorate the disease manifestation of a Leigh's syndrome mouse model. However, subsequent work from the same lab showed that this improvement does not depend on the activation of the proposed pathway, but by alleviating brain hyperoxia. The results do not support the current rationale of this proposal. • The preliminary data are problematic for multiple reasons. One of these is that what the applicant is calling normoxia is actually hyper-oxia. Atmospheric oxygen, at a concentration of 21%, is several-fold higher to what cells experience in most parts of the body. Thus, the experimental approach used does not enable appropriate comparisons. • Preliminary data are limited at testing a single PHD2 inhibitor in patient fibroblasts and showing some improvement. However, no mechanistic insights are shown to explain these effects. The applicants make a suggestion for a possible pathway, but no experimental evidence are reported for this. • The preliminary data do not show that they can do the key experiments.
GWG Votes	Is the proposal well planned and designed?
Yes: 1	*none*
No: 13	• Preliminary studies are done with fibroblasts, making it difficult to extrapolate the results with neurons. • This study will test some inhibitory compounds for PHD2 and assess their effects on mitochondrial functions in patient iPSC-derived neurons. This is a very early stage investigation set up to validate the working hypothesis and describe the beneficial effects of the treatment in vitro. At this stage, it can not be considered for advanced translational applications. • The project is built to test and compare the beneficial effects on mitochondrial functions of selected PHD2 inhibitors in patient derived neural cells. It lacks more breadth to move forward on mouse models that are available for this disease to understand the pharmacokinetics, brain penetration and therapeutic value of the selected compounds. • Growth conditions not well-rationalized. • Concern using fetal cells versus postnatal cells not addressed. • There are major concerns related to the ability to differentiate neurons and use the cells for the proposed experiments. • The neural cell culture system is not designed well. • Making inferences from the behavior of fibroblasts to the behavior of nerve cells is not supportable. Depending on the source of fibroblasts, they may be from an area of the body that is evolved to be able to deal successfully with levels of redox stress that nerve cells do not normally encounter. • The proposal lacks discussion of previous findings from other labs indicating that activation of the molecular hypoxic pathway is not significant for the therapeutic effect of hypoxia in Leigh's syndrome mice. Thus, in light of these results, the findings from in vitro neural cultures might not have relevance in vivo where a more complex tissue metabolic environment might hide or suppress these beneficial effects.

	• There is an absence of discussion of potential pitfalls, particularly in regards to the idea of using a drug that would create a systemic hypoxia response.
GWG Votes	Is the proposal feasible?
Yes: 1	• The proposed plan is feasible considering the expertise of the applicants and the presented preliminary results. • The applicants are experienced scientists with complementary skills and scientific backgrounds covering the major aspects of the present application. • The team is well equipped and have access to the instrumentation and infrastructure to carry out the proposed plan. It is not detailed where the metabolomics by mass spectrometry will be performed, although some preliminary data are shown using this approach. • The budget is fully adequate and well-justified for this experimental program.
No: 13	• Feasibility is questionable - passaging neurons is challenging if they are mature. • Plate reader assays are not sensitive enough for individual cell readouts. • There are major concerns that the experiments cannot be performed in the proposed neural cells. Preliminary data would be required. • The feasibility is impossible to tell due to the number of unanswered questions relevant to the preliminary data. • It's likely that they can do the experiments, but it's not clear that experiments will be successful or worthwhile. • The team does not seem set up to perform the complex experiments that they plan.

Application #	DISC2-12134
Title (as written by the applicant)	Vascularized Cancers for Angiogenesis and Metastasis
Research Objective (as written by the applicant)	This project will develop a microfluidic platform containing stem cell-derived perfusable vasculature and cancer spheroids for screening novel drug candidates.
Impact (as written by the applicant)	Identifying and working with manufacturing companies, product marketing
Major Proposed Activities (as written by the applicant)	• Aim 1 will quantify vasculogenic and angiogenic activity of our stem cell-derived EC subpopulations compared with human umbilical vein endothelial cells (HUVECs). • Aim 2 will generate an angiogenic tumor model by co-culturing human vasculature with spheroids generated from a range of cancers. • Aim 3 will test the platform by quantifying the response of ECs and cancer metastases to a few different angiogenic inhibitors.
Statement of Benefit to California (as written by the applicant)	The research proposed will develop a human organ-on-a-chip platform for screening potential cancer fighting drugs that are expected to accurately predict the ability of new cancer therapies to fight specific cancers. If successful, a new start-up company will be lauched in California that will partner with our current biotechnology industry. The research will also train a postdoc and graduate student in the fields of stem cells and cancer.
Funds Requested	$250,000
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: --

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

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 4	• Current therapies have lack of efficiency. • Important problem. • Conceptual approach not particularly novel.
No: 8	• The need for improved treatment of multiple types of cancers is certainly an unmet need.

	• That said, it doesn't seem like this proposal will add much in addressing this medical need. • Advantages of this relatively complex technology for screening angiogenic and metastatic inhibitors isn't apparent, compared to existing technologies. • The project will not produce a device ready for translation. • Anti-angiogenics have been difficult to come by, however, it is unclear that the assay systems are the issue. These drugs are very toxic, and have off-target effects at the biological level. This system would not address that latter aspect. • The technology is too complex to be used in screening.
GWG Votes	Is the rationale sound?
Yes: 5	• The study builds on prior work in differentiating pluripotent stem cells to endothelial cells and using these in microfluidic devices. • hPSC-derived ECs have potential applications in identifying new angiogenesis targets as potential cancer therapeutics. • HUVECs have many problems that might be overcome with endothelial cells • Co-culture approaches might lead to insight into migration patterns that might be "rescuable" with drugs
No: 7	• The rationale is moderate. Data or literature that would suggest hPSC-derived ECs would be superior is unclear. In addition, deficiencies in HUVEC for angiogenesis, and data to suggest that all cancer types being tested are worthy of consideration is not well supported. The need for improved systems is clear, but whether this requires micro-laboratory technology, is less so. • It is not particularly clear that this project requires stem cell technologies, although the authors are using stem cell derived endothelial cells. • Strong data to support the ideas of imaging, and quantitative measure of angiogenesis. The results however with human cells, the efficiency, and whether human cells are even needed vs. murine models is unclear. This system could work with established mouse ESC derived ECs. • Concern around the length of time required for EC maturation and why KDR+ cell sorting is required. • The sphere formation that occurs from culturing methods is unclear. • There is a great deal of critical preliminary data missing from this application. • Because so much data is missing, this is not clear. • The application does not seem appropriate.
GWG Votes	Is the proposal well planned and designed?
Yes: 1	• Aims depend on each other • Quantification is an issues - i.e what is the cut off for "robust"? • Not enough relevant preliminary data
No: 11	• The complexity of the device doesn't match the need for a screening tool. This appears better suited to identifying mechanisms of crosstalk between cancer and ECs. • There is not a proof-of-concept demonstrating advantages of this device over competing technologies. • The aims, sequence of experiments, procedures, and tools eg. infrastructure, capacity, and plan are excellent and well designed. • The quantitative nature of the imaging analysis for angiogenesis and tumor evasion is superior. However, this is very unique and will be difficult for future users if the project is successful. • Although they demonstrate that they can make the cells, there is no information relevant to the cancer-focused goals of the application, and no demonstration that this approach is an improvement over the use of existing cells. In fact, figure 5 on the quantification of new vasculature shows experiments conducted with standard HUVECs. • The work is laid out well, and everything has been proven to be in place to execute. The use of tumor cells, creation of sphere, and integration with ECs derived from human PSC is less clear, and how the decision will be refined. • Why diverse iPSCs are required, and how many need to be tested for the purposes of the application? What if specific iPSC types or culture conditions are better than others? How will this be interpreted into the final system used for identification of drugs? • The microfluidic system does not seem state-of-the-art.
GWG Votes	Is the proposal feasible?
Yes: 4	• The PI has the expertise with stem cells, ECs, and microfluidics needed to perform the proposed study.

	• Maybe -Purification of cells is challenging with low yield and long culturing time raising questions of scalability • No concerns with their team
No: 8	• Aim 2 requires assessment of several tumor spheres, not all will work, and how this will be prioritized, is unclear. In addition, the human EC generation from PSCs seems to require 46 days. It is difficult to know the quantify of cells that can generated, how many microfluidic chambers will be required to draw a conclusion, and how many tumor types from Aim 2 will tested and migrated to Aim 3. No information on this calculation, capacity or scale up was provided. • The applicant mentions “robust” however, it is unclear how this will be gauged or measured. Against what exactly? • Evidence that the microfluidics model will translate over to human clinical results is unclear, and the use of compounds and choice to this point in Aim 3 need to be refined. There is concern that system does not provide a surrogate for tumor metastases. • This is far from being relevant to translation.

Application #	DISC2-12151
Title (as written by the applicant)	Hematopoietic Stem Cell Extracellular Vesicle-Mediated RNAi to Target Oncogenes
Research Objective (as written by the applicant)	We propose genetically engineering blood-forming stem cells to secrete RNA in small packages that will be taken up by cancer cells and disrupt the mutations that drive that specific cancer.
Impact (as written by the applicant)	If successful, this would enable us to inactivate cancer-specific genes. By intervening on the mutations that drive cancer, we can address the basis of cancer directly.
Major Proposed Activities (as written by the applicant)	• We will test if these packages can be internalized by cancer cells and cause degradation of cancer genes. This will take place in cells grown in the lab. • Using packages grown in the lab, we will inject these into mice bearing human cancer cells and test cancer gene degradation. • We will engineer blood-forming stem cells to secrete packages to degrade cancer genes, then transplant these cells into mice with human cancer and determine the effects.
Statement of Benefit to California (as written by the applicant)	If successful, we will immediately translate this technology to a California startup therapeutic company. This would bring revenue to the state of California. We would also prioritize California sites for the clinical trial, giving Californians the opportunity to benefit from the treatment, if within their goals of care.
Funds Requested	$249,998
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: --

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

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

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 1	*none*
No: 11	• The approach has low likelihood of success and thereby has a low impact in the field. • The approach is unlikely to improve patient care. • RNAi produced by cells has been found to be too unstable for therapeutic value. • Not well outlined.
GWG Votes	Is the rationale sound?

Yes: 0	*none*
No: 12	• Genetically engineering hematopoietic stem cells (HSCs) are to be used to secrete antisense RNA in their extracellular vesicles to target oncogenes in cancer. • Fundamental problems with the approach recognized in the field are not considered. • No preliminary data is presented. • No preliminary data. • Not enough preliminary data to support the rationale. • Unclear how vesicles are optimized.
GWG Votes	Is the proposal well planned and designed?
Yes: 0	*none*
No: 12	• The approach is unlikely to work and no preliminary data are presented to persuade otherwise. • The timeline is sparse. • Evaluation of whether the approach was successful is not clear. • Too many technologies without enough focus. • Labeling techniques are unclear. • Pitfalls and alternative approaches are presented, but with no preliminary data, and so many likely ways to fail discussed, it is not clear how recognition of pitfalls will guide progress.
GWG Votes	Is the proposal feasible?
Yes: 1	• Experimental details are lacking- i.e why is a mouse model used, missing controls, how are samples collected etc
No: 11	• Milestones are indicated but barely discussed. • PI is the director of the Chimeric Antigen Receptor (CAR) T-Cell Program at their institution. Other team members are to be determined. • Facilities are excellent. • The budget is appropriate for the research proposed. • Many concerns with the approach.

Application #	DISC2-12096
Title (as written by the applicant)	Identifying Exposure to SARS-CoV-2 using Novel Peptide Antigens to Elicit CD8+ T Cells
Research Objective (as written by the applicant)	A set of peptides that elicit CD8+ T cells that will be the basis for COVID-19 diagnostics and a method for detecting these T cells.
Impact (as written by the applicant)	Accurately identifying who has been infected by SARS-CoV-2 has been a major problem. This work will provide a reliable method to detect these patients.
Major Proposed Activities (as written by the applicant)	• Isolate CD34+ HSCs from COVID-19 patients • Perform AIM and ICS assays • Evaluation of Tetramer staining vs IGRA assays • Blinded evaluation of COVID-19 samples
Statement of Benefit to California (as written by the applicant)	COVID-19 is the greatest health and economic challenge California has ever faced. Understanding who has been infected and what percent of the population has been infected are critical to determining when the economy can return to full force. This has been difficult to know based on current PCR and antibody tests. By providing a test that can be applied to patients even months after being infected, whether asymptomatic or severely infected, we can accurately understand the breadth of COVID-19.
Funds Requested	$250,000
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: --

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

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

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 2	• Innovative. • Could have niche applications.
No: 12	• The applicant proposes to develop a T cell-based diagnostic assay to identify COVID-19 positive patients. The applicant overstates the problem of sensitivity related to antibody based tests. The solution proposed is not more sensitive than current approaches and introduces significant artifacts that will hinder experimental interpretation. • It is very unlikely that this CD8+ T cell-based test will outperform antibody tests for detection of past exposure to SARS-CoV-2 because it is based on a flawed approach.

	• The premise of the application and the experimental plan are both fundamentally flawed. Unlikely to result in useful information. • The proposed diagnostic does not provide an increased sensitivity for SARS-CoV-2 infection. • ELISA-based antibody tests are adequate based on new literature. • Approach is complex and potentially expensive thus not very translational.
GWG Votes	Is the rationale sound?
Yes: 0	*none*
No: 14	• The applicant overstates the weaknesses of antibody tests and does not mention the false positives that could be caused by CD8+ T cells specific for peptides shared by common cold Coronaviruses and SARS-CoV-2. • Although peripheral blood from a SARS-CoV-2-infected person should contain numerous S peptide:HLA-specific CD8+ T cells because of the clonal expansion of naïve T cells, the CD8+ T cell population generated from HSCs from that person will, in the best of circumstances, be representative of the pre-immune repertoire in which S peptide:HLA-specific T cell will be very rare. No simple assays exist to measure these rare cells before clonal expansion. • The formation of a peptide-specific, HLA-restricted T cell repertoire depends on specialized antigen-presenting cells in the thymus. These cells are not present in the culture system used to generate CD8+ T cells from HSCs in vitro. It is not clear that a normal T cell repertoire can be generated this way. • The HSC-derived naive CD8+ T cells are unlikely to be successful and even if they were they will not reflect the normal elicited repertoire. There are much cheaper and accurate ways to generate this info. • The major concerns are that the applicants will attempt to identify immunogenic spike protein peptides using HSC derived CD8+ T cells. Technically, differentiating HSCs into CD8+ T cells is not a validated approach. Biologically, natural memory T cells do not derive from HSCs. This grant does not recapitulate natural viral immunity. • The biology is flawed, in principle.
GWG Votes	Is the proposal well planned and designed?
Yes: 0	*none*
No: 14	• It is hard to argue that the proposal is well designed given the flaw of using HSC-generated CD8+ T cells to screen for SARS-CoV-2 S peptide epitopes. • No, the assays described are unlikely to work or provide useful info. • This proposal is not designed in a way that can recapitulate natural antiviral immunity. • No - many problems with the rationale and biology.
GWG Votes	Is the proposal feasible?
Yes: 0	*none*
No: 14	• As stated above, HSC-generated CD8+ T cells will not allow detection of SARS-CoV-2 S peptide:HLA-specific T cells. • The proposal is not feasible. • The differentiation seems difficult.

Application #	DISC2-12156
Title (as written by the applicant)	Superiority of BACS automated isolation of CD34+ cells in sterile "functionally closed" process cartridge over manual, "open system" Ficoll/MACS.
Research Objective (as written by the applicant)	We propose to discover that CD34+ cells can be recovered by the BACS technology after being buoyantly isolated by BACS reagent and then harvested after this buoyancy ends, retain their full function.
Impact (as written by the applicant)	Manufacturing costs and labor time should be significantly less than conventions Ficoll/MACS processing
Major Proposed Activities (as written by the applicant)	● Detailed system level product renderings, diagrams and 3D digital models at various levels of detail, preliminary bill-of-material (BOM), system controls, sensors, electronics and interfaces. ● A comprehensive documentation package including all detail drawings, assembly drawings, purchased hardware component data sheets package, parts lists, applicable work or assembly instructions. ● Assemble three prototype X-Buoy Systems. ● Utilizing the data from all project phases, design, develop and re-develop the various firmware aspects for the product. • X-Buoy System controller firmware. ● Test prototype with viable CD34 cells sourced from cord blood ● Assemble 1st production run of 25 units and QC the performance
Statement of Benefit to California (as written by the applicant)	It is the opinion of most, if not all, California citizens that medicine, perhaps especially stem cell medicine, is too expensive for all of us, and priced out of reach of all individuals who have no health insurance. BACS technology would double or triple the efficiency of isolating the purified stem cells, and immune cells, for clinical cell therapy treatments compared to the conventional technology being practiced now. This should lead to lower costs of stem or immune cell therapies
Funds Requested	$180,200
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: --

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

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 3	• There is a need for novel cell enrichment and selection methods for cell therapies and regenerative medicines. • The proposal attempts to develop a novel cell selection approach that could be broadly applicable for the field. • Improving efficiency of isolating cells would be a progress in the field. • Incremental improvement. • Not novel.
No: 11	• The proposal was too poorly written, without enough intellectual discussion of the principles of their device.
GWG Votes	Is the rationale sound?
Yes: 1	*none*
No: 13	• The concept of buoyancy based methods is not a validated concept. It's unclear how they'll get true cell selectivity and specificity compared to a more standard magnetic based isolation methods. • Prototype development is a valid goal.
GWG Votes	Is the proposal well planned and designed?
Yes: 1	*none*
No: 13	• There is no clear path or plan to go from product concept to reality. • Reads more like a marketing brochure than a solid scientific proposal. • No preliminary data.
GWG Votes	Is the proposal feasible?
Yes: 1	*none*
No: 13	• It is unclear if the project is feasible because the applicant provides no preliminary data. It's unclear if this concept is feasible. • Not clear as no data are provided. • No clear path provided to a product.

Application #	DISC2-12166
Title (as written by the applicant)	Activation of Endogenous Stem Cell Repair After Myocardial Infarction
Research Objective (as written by the applicant)	A therapeutic protein to recruit and activate endogenous stem cells for treatment of acute myocardial infarction
Impact (as written by the applicant)	Limiting the initial ischemic damage from acute myocardial infarction leading to the development of congestive heart failure
Major Proposed Activities (as written by the applicant)	• Demonstrate the binding properties and recruitment of human stem cells by the candidate in vitro • Characterize the ability of the candidate to improve left ventricular ejection fraction in a rat model of ischemia/reperfusion • Determine the therapeutic mechanisms of action in restoring ventricular function in a rat model of ischemia/reperfusion • Demonstrate recruitment of human stem cells to infarcted myocardium in a rat model of ischemia/reperfusion
Statement of Benefit to California (as written by the applicant)	Heat disease is the leading cause of death in the State of California with 62,797 deaths in 2017. The severity of damage due to a first myocardial infarction is a major determinant of mortality due to heart failure. Therefore, the goal of this research is to develop a novel therapy to limit the degree of initial damage in order to improve survival and quality of life
Funds Requested	$249,914
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: --

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

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

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 1	• Important disease.
No: 13	• This is highly unlikely since literature indicates that adult cardiac regeneration is virtually non-existent. • The proposal is very early stage. No evidence that this strategy may work. • Seriously flawed proposal. While it is meant to address a major unmet medical need, the evidence that unspecified "endogenous stem cells" can be recruited to enhance repair at

	sites of cardiac ischemic injury is severely limited, despite scores of basic and clinical studies over nearly 2 decades. ● The applicant presents designs for protein constructs. Criteria for achievement of milestone #2 (beyond the statement of the activity to "Evaluate the therapeutic activity in a rat model of infarction/re-perfusion") are not presented. Thus, neither the minimal criteria for a candidate nor the algorithm to select the best among multiple constructs is clear. ● Delivery isn't likely to be the key limiting factor in scores of previous studies of cardiac cell therapy, and there's no evidence given that the proposed constructs could capture more useful cells either from within the heart or from more distant sites.
GWG Votes	Is the rationale sound?
Yes: 0	*none*
No: 14	● Considering the robust literature in the last decade documenting that adult cardiac regeneration is extremely limited, the scientific rationale is flawed. ● The proposal derives heavily from a prior report from the lab of the PI's main collaborator. They reported beneficial effects in the ischemia/reperfusion model of a bifunctional anti-myosin/anti-CD45 antibody in rats given human hematopoietic stem cells. The biological basis of that activity was not explained. Early notions that HSCs could differentiate to cardiomyocytes have long been discredited. ● Regenerative potential in the heart is very limited. ● Cells are not characterized. ● Totally unclear what stem cells the constructs are designed to capture. Various types of MSCs have been tested exhaustively in cardiac models/patients, with at best modest, transient effects. Endogenous cardiac stem cells are a vexed topic, at best - and no evidence indicates the proposed constructs would enhance recruitment or activity of such cells (assuming they even exist). ● Published data from 2010 does suggest enhanced vascularization in the ischemia/reperfusion model mediated by certain peptides linked to an anti-myosin mAb. However, overall the preliminary data are far from compelling and give no hint of biological specificity or of the specific cells sought to be recruited. Pro-inflammatory cells might be recruited and actually have a negative effect. ● The premise of the grant is incorrect regarding regeneration in the heart.
GWG Votes	Is the proposal well planned and designed?
Yes: 0	*none*
No: 14	● Low quality project. ● Approach not clear with many details lacking. ● No compelling data. ● Criteria for success are not well defined, and the project lacks a mechanistic framework to select a therapeutic candidate. ● Project is so unfocused that it does not meet CIRM's urgency criterion.
GWG Votes	Is the proposal feasible?
Yes: 0	*none*
No: 14	● Besides the flawed premise (as discussed above), I do not think they will be able to complete all proposed work in one year. ● There is no evidence of collaborators with expertise in stem cells and in vivo assessment of regeneration. ● The milestones are stated as activities/tasks. It's possible that some biological effects will be observed, but the chances of developing a translatable candidate appear very slim. ● Team has reasonable expertise in recombinant protein construction and in cardiac physiology. Other aspects of the biology, especially relating to stem & progenitor cells, would benefit from strong consultant(s) / collaborator(s).