DISC 2, Round 1 2017

$18,977,751 GWG RECOMMENDED

APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Score Range Low	Score Range High	GWG Votes Y	GWG Votes N	Re-submission	Previous CIRM Funding	Disease Indication or Applicability	Product Type	Approach
DISC2-10088	Preclinical development of AAV vector-mediated in vivo hepatic reprogramming of myofibroblasts as a therapy for liver fibrosis	$1,638,389	Y	91	92	4	85	95	12	0	N	Y	Liver fibrosis/cirrhosis	Gene therapy	In vivo delivery of vector to reprogram myofibroblasts to hepatic cells
DISC2-10110	Multipotent Cardiovascular Progenitor Regeneration of the Myocardium after MI	$1,817,654	Y	90	92	3	90	95	13	0	Y*	Y	Heart failure	Cell therapy	iPSC derived cardiac progenitor cells
DISC2-10090	Human Cardiac Chip for Assessment of Proarrhythmic Risk	$944,721	Y	90	90	3	83	95	10	1	Y	Y	Drug cardiotoxicity screening	Drug discovery tool	Drug screening platform using human iPSC-derived cardiomyocytes
DISC2-10124	Targeted Gene Editing in the Treatment of X-Linked Hyper-IgM Syndrome	$1,665,908	Y	90	90	1	90	92	15	0	Y	N	X-linked hyper-IgM syndrome	Gene-modified cell therapy	Genetic modification of autologous hematopoietic cells for transplant
DISC2-10061	Lgr5-mediated self-renewal in B cell selection and leukemia-initiation	$2,186,520	Y	90	89	3	80	90	14	1	N	Y	B cell tumors	Biologic therapy	Antibody-drug conjugate that targets cancer stem cells
DISC2-10120	Microenvironment for hiPSC-derived pacemaking cardiomyocytes	$2,042,728	Y	90	89	2	84	90	12	1	Y*	Y	Cardiac arrhythmia	Cell therapy	iPSC derived pacemaker cardiomyocytes
DISC2-10195	Identification and characterization of the optimal human neural stem cell line (hNSC) for the treatment of traumatic brain injury (TBI) 2.0.	$1,671,213	Y	85	86	9	75	100	8	7	Y*	Y	Traumatic brain injury	Cell therapy	Efficacy comparison of 4 GMP neural stem cell products
DISC2-10182	Discovery of therapeutics for Huntington's Disease	$1,399,800	Y	85	83	9	65	95	9	5	Y	N	Huntington's disease	Drug discovery tool	Drug screening platform using human embryonic stem cells
DISC2-10067	A tool for rapid development of clinical-grade protocols for dopaminergic neuronal differentiation of Parkinson's Disease patient-derived iPSCs	$677,160	Y	85	82	8	60	90	8	7	N	Y	Parkinson's disease	Cell production tool	Tool to optimize production of GMP-grade dopaminergic neurons from iPSC and hESC
DISC2-10129	Non-Toxic, Highly-Effective Bioinspired Cryoprotectants for On-Demand Stem Cell Therapies	$887,883	Y	85	82	7	60	90	8	7	N	N	Cell cryopreservation	Cell cryopreservation medium	Develop a non-toxic, peptoid based cryoprotectant for stem cell therapies
DISC2-10188	Immunization strategies to prevent Zika viral congenital eye and brain disease	$2,206,291	Y	85	82	4	75	85	8	6	N	N	Zika virus infection	Vaccine discovery tool	Tool using human iPSC-derived neural and ocular cells to identify Zika virus vaccine candidates
DISC2-10107	A Novel Approach to Eradicate Cancer Stem Cells	$1,839,484	Y	85	76	16	50	92	6	6	N	N	Colorectal cancer	Small molecule	Screen small molecule candidates for effectiveness against colorectal cancer stem cells
DISC2-10134	Platform Technology for Pluripotent Stem Cell-Derived T cell Immunotherapy	$1,062,076	N	84	83	3	75	86	3	12	N	Y	Cancer	Cell immunotherapy	Generate T cells that target tumors from pluripotent stem cells
DISC2-10142	Development of PEG-PTN for Hematopoietic Regeneration	$951,920	N	83	82	5	75	90	7	8	N	Y			
DISC2-10162	Development of Vasculature from iPSCs	$2,141,519	N	80	81	2	80	85	1	14	N	N			
DISC2-10099	Towards hepatocyte cell replacement therapy: developing a renewable source of human hepatocytes from pluripotent stem cells	$2,201,136	N	80	80	7	70	93	6	9	Y	N			
DISC2-10092	Nomination of a clinically approved drug that inhibits the Rho kinase pathway for treatment of intellectual disability associated with OPHN1 Syndrome	$405,750	N	80	79	4	70	84	0	15	N	N			
DISC2-10050	Develop iPSC-derived microglia to treat progranulin deficient Frontotemporal Dementia	$1,929,714	N	78	78	3	75	83	0	14	N	N			
DISC2-10085	Stem Cell-based Modeling and Therapeutic Targeting of IDH Mutant Gliomas	$2,192,183	N	75	77	9	60	90	3	12	N	N			
DISC2-10191	Engineered mesenchymal stem cells for combinatorial cancer immunotherapies	$1,803,602	N	75	76	4	70	85	1	14	N	N			
DISC2-10055	Cross-correction of lysosomal storage diseases and leukodystrophies through autologous transplant of genetically modified hematopoietic stem cells	$1,268,455	N	75	75	5	70	84	0	15	N	N			
DISC2-10203	Dynamic scaffolding system to enhance lineage-specific differentiation and downstream functionality of induced pluripotent stem cells	$804,254	N	75	75	3	70	85	1	14	Y	N			
DISC2-10093	Human iPSC-based phenotypic screening tool development for drug identification in Parkinson's disease	$1,191,960	N	71	72	2	70	75	0	12	N	Y			
DISC2-10199	Development of a new therapeutic for directing target specific stem cell migration and treatment	$1,906,900	N	70	67	8	55	80	0	14	N	Y			
DISC2-10205	A synergistic stem cell therapy for juvenile macular dystrophy	$1,828,023	N	70	67	4	60	70	0	12	N	Y			
DISC2-10161	Preclinical testing of retinal tissue from clinical-grade human embryonic stem cells for vision improvement in Rdy/+ cats with retinal degeneration	$1,283,199	N	65	67	7	55	80	0	15	N	N			

APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Re-submission	Previous CIRM Funding	Disease Indication or Applicability	Product Type	Approach
DISC2-10213	Engineering Live Meniscus Tissue by Electrospinning and Electrospraying Stem Cells	$1,886,146	N	65	66	3	65	75	0	14	N	N			
DISC2-10193	Stem cell derived exosomes to ameliorate cancer therapy-induced normal tissue injury in the brain	$1,398,794	N	65	64	4	50	65	0	15	Y	Y			
DISC2-10057	SF-Heps: Induced Hepatocytes Scalably Produced from Lipoaspirate Adipocyte Stem Cells as Regenerative Therapy for Acute Liver Disease	$1,388,163	N	60	70	15	55	95	5	9	N	N			
DISC2-10189	Developing scaling-up differentiation of functioning hepatocytes from hESC using iCELLis bioreactor system	$2,155,040	N	60	60	9	40	75	0	14	N	N			
DISC2-10108	ADAR1 Enhanced Expansion of Self-renewing Human Hematopoietic Stem Cells	$2,167,200	N	-	-	-	-	-	0	13	N	Y			
DISC2-10176	Bioprinting A Patch for Cardiovascular Repair	$1,831,499	N	-	-	-	-	-	0	15	N	N			

Application #	DISC2-10050
Title (as written by the applicant)	Develop iPSC-derived microglia to treat progranulin deficient Frontotemporal Dementia
Research Objective (as written by the applicant)	Develop stem cell-based therapy to treat dementia
Impact (as written by the applicant)	There are no treatments for dementia. If successfully achieved, this study will lead to a cure of a familial form of dementia in the elderly population.
Major Proposed Activities (as written by the applicant)	• Develop a robust human stem cell-derived microglial platform for cell-based therapy • Determine short-term safety and efficacy of engrafted human microglia in wildtype mice • Determine short-term efficacy of engrafted human microglia in FTD mouse models • Determine long-term efficacy of engrafted human microglia in FTD mouse models
Statement of Benefit to California (as written by the applicant)	The proposed research will benefit the State of California and its citizens because of the potential to cure a major form of dementia in the elderly population. With the fast aging population in California, more and more Californians are diagnosed with neurodegenerative dementias. There is an urgent need to develop a treatment or cure for these devastating conditions. Success of our study will address this urgent medical challenge of our modern society.
Funds Requested	$1,929,714
GWG Recommendation	***Not recommended for funding***

Scoring Data

Final Score: 78

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

Mean	78
Median	78
Standard Deviation	3
Highest	83
Lowest	75
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	8	1	5
Is the rationale sound?	1	4	9
Is the proposal well planned and designed?	1	5	8
Is the proposal feasible?	0	5	9

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- Frontotemporal dementia is a serious medical problem. It appears to be largely familial and mutations in progranulin (PGRN) represent 10-20% of these cases.
- Enhancing PGRN levels by transplanting microglia may alleviate the disease.
- Preliminary evidence that PGRN deficiency in knock out mice causes multiple brain deficiencies is strong.
- The preliminary data presented is convincing and of high quality. The team has advanced quite a bit into their work of differentiating and characterizing i3-MG and iMG cells which will allow them to perform the proposed work.

Concerns

- Proposal lacks mouse microglia human ESC controls.
- It is not clear if other forms of FTD or dementia can be treated with microglia.
- The mouse model is somewhat artificial in conditionally inducing PRGN deficiency at 3 months of age.
- The ability to generate the key cells is lacking. If this aim doesn't work, the whole proposal doesn't work. This is particularly important as microglia can be beneficial or harmful, and it is not known what the cells of interest will do.
- It appears the transplantation is carried out early after conditional PGRN, yet dementias have ongoing damage and change occurring. In the clinical situation, the patient may have been affected by PGRN deficiency for years.
- The anticipation and concern about pitfalls seems somewhat limited considering the exploratory nature of the application.
- A key concern is that the proposal does not consider a critical scenario wherein the implanted microglia, along with resident cells, could pick up the pathological proteins (Tau, TDP43) and spread them to healthy cells throughout the brain in a prion-like fashion, as it has been shown with the mutant huntingtin protein in a drosophila model (Babcock et al. PNAS, 2015). The fact that microglia are known for the migratory potential makes this particularly worrisome.
- While the applicants admit to having used short-term immunosuppression to avoid graft rejection in their animal model, they do not specify how long this lasted. This is of critical importance as it could have significant consequences. The immune response could occur in waves that risks activating the implanted microglia. This is a crucial concern as in humans, there is likely to be a chronic inflammatory response due to the disease itself as well as because of the transplant.
- Given the function of microglia in realms other than inflammation (e.g. synaptic pruning), it is unclear how injecting several microglial cells would not affect other normal brain functions.

Application #	DISC2-10055
Title (as written by the applicant)	Cross-correction of lysosomal storage diseases and leukodystrophies through autologous transplant of genetically modified hematopoietic stem cells
Research Objective (as written by the applicant)	We seek to develop hematopoietic stem cell gene therapy approaches to treat the enzyme deficiencies GM1 gangliosidosis, Niemann-Pick, and Canavan disease.
Impact (as written by the applicant)	The development of these therapies would create a treatment for GM1, Niemann-Pick, and Canavan diseases which currently have no cure or effective therapy to halt progression of these diseases.
Major Proposed Activities (as written by the applicant)	• Develop and manufacture the lentiviral vectors for use in our proposed experiments. • Evaluate the safety of our therapeutic candidates in human CD34+ cells in CFU assays and the subsequent derivation of their immune cell progeny. • Evaluate the feasibility of our therapeutic candidates in in vitro efficacy experiments using chemical substrates. • Develop immunodeficient mouse models of GM1 gangliosidosis, Niemann-Pick, and Canavan diseases for the acceptance of human cells for transplant and engraftment. • Evaluate the in vivo efficacy of our therapeutic candidates in the immunodeficient disease-specific mouse models. • Evaluate the in vivo safety of our therapeutic candidates in an immunodeficient mouse model.
Statement of Benefit to California (as written by the applicant)	Lysosomal storage diseases and leukodystrophies are genetic diseases that affect the central nervous system and other major organs. Currently, there are no cures and palliative care only marginally improves patient's lives. Enzyme replacement therapy is available, however, this approach does not effectively enter the CNS. By using the immune system to deliver the wild type enzymes systemically, affected cells would uptake the proteins, including in the CNS through expression from microglia.
Funds Requested	$1,268,455
GWG Recommendation	***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 average of the individual member scores. Additional parameters related to the score are shown below.

Mean	75
Median	75
Standard Deviation	5
Highest	84
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	10	4	1
Is the rationale sound?	8	4	3
Is the proposal well planned and designed?	2	8	5
Is the proposal feasible?	0	10	5

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The project plan is straightforward.
- AAV correction of HSCs from a patient is very attractive for multiple reasons.

Concerns

- It is unclear whether the animal models will be relevant.
- The timeline does not appear to be feasible.
- Feasibility is a major weakness for this application.
- For two of these diseases there are pharmacological agents that are quite advanced and it seems to be important to determine whether this proposed approach is as, more or less effective than such easy-to-implement approaches.
- The transplantation shortly after birth is a concern. Pre-symptomatic HSC transplantation in a related disease, Krabbe disease, is of questionable value in part due to concerns about morbidity of the HSC transplantation approach.
- Diseases that can vary greatly in the time of presentation and thus, it seems important to ask the question of whether treatment at the time the earliest symptoms is actually efficacious.
- The fact that GM2 levels are not falling to the levels of a heterozygote was a definite concern.

Application #	DISC2-10057
Title (as written by the applicant)	SF-Heps: Induced Hepatocytes Scalably Produced from Lipoaspirate Adipocyte Stem Cells as Regenerative Therapy for Acute Liver Disease
Research Objective (as written by the applicant)	SF-Heps: a liver cell therapy generated from fat cells from liposuction surgeries to regenerate the livers of patients with liver disease
Impact (as written by the applicant)	SF-Heps could be an effective regenerative medicine therapy for the treating patients with liver disease by providing cells that behave like liver cells that can regenerate a whole liver.
Major Proposed Activities (as written by the applicant)	• Determine whether SF-Heps behave like human liver cells when cultured in a dish • Determine whether SF-Heps can regenerate the livers of mice that undergo liver damage • Determine the properties that ensure SF-Heps to be the highest cell yield and cell quality for the treatment of patients • Determine the first use where SF-Heps will be used in patients in a clinical trial and chart the path for which SF-Heps will be used in patients with several types of liver disease
Statement of Benefit to California (as written by the applicant)	Liver failure is an often deadly condition with multiple causes and significant prevalence in the US and California. Liver transplant is often the only cure but is in scarce supply compared to high demand. New therapies are needed. SF-Heps is a stem cell therapy that can provide large amounts of liver-like cells to regenerate diseased livers. This research will determine whether SF-Heps can regenerate livers in pre-clinical models and then develop this therapy for liver disease patients.
Funds Requested	$1,388,163
GWG Recommendation	***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 average of the individual member scores. Additional parameters related to the score are shown below.

Mean	70
Median	60
Standard Deviation	15
Highest	95
Lowest	55
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	5
(1-84): Not recommended for funding	9

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	9	3	2
Is the rationale sound?	2	9	3
Is the proposal well planned and designed?	4	7	3
Is the proposal feasible?	1	10	3

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- Excellent product design.
- Excellent use of collaborators.

Concerns

- Little rationale is provided that “trans-differentiation” to hepatocytes from the fat tissue is feasible.
- No preliminary data demonstrating feasibility and validity of differentiation to hepatocytes from the fat tissue is provided.
- Experimental details and plan are sketchy and are not well thought out.
- The data showing that fat cells can differentiate into fully functioning hepatocytes are not convincing.
- Most of the experiments will be subcontracted, making feasibility more risky.
- The clinical focus of the application is interesting but it should be based on other cell types.
- Properly cultured iPSC do not form tumors after transplant - these appear to be mishandled, and undercuts the rationale of the proposal.
- It is uncertain whether fat-derived cells are the best source for hepatocytes.
- The hepatocyte differentiation procedure was not adequately explained; how it was done and what materials were used. Even though the patent was furnished, some reviewers were skeptical regarding the process- perhaps a brief summary would be helpful.
- Some reviewers believed that the tumorigenic aspect was not that important and more attention was drawn to the lack of extensive functional and genomic characterization of the differentiated cells, i.e. limited information on TAT, FAH, CYP3A4, FBG, HGD, HPD, ARG1 and CYP3A4 activity.
- In an FRG model, survival when compared to primary hepatocytes would also be supportive. While the first milestone comparator to primary hepatocytes was laudable, subsequent studies running primary hepatocytes as the positive control would provide strength.

Application #	DISC2-10061
Title (as written by the applicant)	LGR5-mediated self-renewal in B cell selection and leukemia-initiation
Research Objective (as written by the applicant)	LGR5-antibody drug conjugate to target LIC in B cell tumors that undergo self-renewal
Impact (as written by the applicant)	LIC were only defined in myeloid leukemia, while LIC populations in B cell tumors remain elusive. LICs give rise to drug-resistance and relapse and remain unsolved clinical problems in B cell tumors.
Major Proposed Activities (as written by the applicant)	• Proof of concept studies- Positive selection by antigen-receptor (BCR) signals drives self-renewal in normal B cell development and leukemia and lymphoma. • Define patient groups and B cell leukemia and lymphoma subtypes that will benefit from LGR5-ADC mediated eradication of LIC. • Safety and efficacy profiles - choice of LGR5-ADC based on safety and efficacy profiles in quiescent Lgr5+ populations • In vivo testing platform –optimizing LGR5-ADC efficacy and therapeutic window • IND-enabling studies, concept for multicenter phase 1 clinical trial to test safety and tolerability of LGR5-ADC in patients with pre-B ALL and mature B cell lymphoma.
Statement of Benefit to California (as written by the applicant)	B cell tumors account for an estimated ~129,000 newly diagnosed patients in 2015 in the US and California. Despite improvements, survival rates recently leveled off near 60%. 40,000 patients are expected to die from B cell tumors in the US and California this year. 1.2 million people are currently living with or recovering from B cell tumors. Therefore, stem cell-based efforts to reduce toxicity and minimize late effects are an important aspect in the development of new therapy strategies.
Funds Requested	$2,186,520
GWG Recommendation	***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 average of the individual member scores. Additional parameters related to the score are shown below.

Mean	89
Median	90
Standard Deviation	3
Highest	90
Lowest	80
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	1

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	12	2	1
Is the rationale sound?	13	1	1
Is the proposal well planned and designed?	12	0	3
Is the proposal feasible?	11	1	3

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The potential therapeutic impact and the strength of the preliminary data are overwhelming.
- Compelling data regarding self-renewal in B cell malignancies.
- Drug is already in hand.
- Preliminary data in Figs 14 and 16 indicate targeting LGR5 would drastically improve survival for B-cell leukemia and lymphoma patients with elevated LGR5 expression.
- Strengths are in the preliminary data and rationale.

Concerns

- Relevance in humans questioned.
- Aim 1 will not impact ultimate utility of the product.
- There is no discussion regarding LGR5+ normal stem cells and potential toxicities.
- Long-term effect of targeting LGR5 on endogenous stem cells in the gut, skin, and other tissues must be further characterized to assess potential harmful side effects in humans.
- If LGR5 is required for ALL propagation, there's a concern for stimulating aggressive ALL by inducing high expression of LGR5.

Application #	DISC2-10067
Title (as written by the applicant)	A tool for rapid development of clinical-grade protocols for dopaminergic neuronal differentiation of Parkinson's Disease patient-derived iPSCs
Research Objective (as written by the applicant)	Develop a tool that facilitates rapid, cost effective development of optimized GMP-grade hPSC differentiation into functional DA neurons and apply this device to a cohort of PD patient-derived iPSCs.
Impact (as written by the applicant)	Creating GMP-grade, functionally consistent phenotypes for DA neurons from each patient will significantly increase the likelihood of stem cell-derived DA neuron-based therapy for PD sufferers.
Major Proposed Activities (as written by the applicant)	• Develop a microfluidic device platform and approach that enables high-throughput optimization of a multistage, multifactor differentiation protocol. • Validate these new tools with the gold standard WA09 hESC line and the current best performing patient iPSC line using our research-grade DA neuronal differentiation protocol. • Transition research-grade protocol to GMP-grade protocol with gold standard WA09 hESC line and the current best performing patient iPSC line • Implement the tool to achieve optimized GMP-grade differentiation conditions for the generation of phenotypically and functionally equivalent DA neurons from eight PD patient iPSC lines. • Translate optimized GMP-grade differentiation conditions for each cell line to larger scale tissue culture plate/flask-based cultures and characterize using genomic analysis and electrophysiology.
Statement of Benefit to California (as written by the applicant)	Thousands of Californians suffer from the degenerative effects of Parkinson's disease, a disease for which there is no cure. Our study seeks to develop a tool to accelerate the clinical assessment of a possible solution for PD sufferers, the production of neurons that can be used treat PD patients with cells derived from their own stem cells. The same approach may be applied to other diseases, such as diabetes and heart disease, to the benefit of many of the citizens of California.
Funds Requested	$677,160
GWG Recommendation	***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 average of the individual member scores. Additional parameters related to the score are shown below.

Mean	82
Median	85
Standard Deviation	8
Highest	90
Lowest	60
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	8
(1-84): Not recommended for funding	7

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	13	0	2
Is the rationale sound?	7	5	3
Is the proposal well planned and designed?	6	4	5
Is the proposal feasible?	3	7	5

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- There is enough evidence to foresee cell replacement therapy as a viable treatment option for this disease, as initial transplantation studies using fetal ventral mesencephalic cells yielded benefits in a number of cases.
- This proposal is extremely rigorous in its approach to produce large-scale, clinical-grade cells for cell replacement therapy in PD. The applicants carefully discuss all the problems that this field has faced to this day and have properly tackled several of these issues.
- The preliminary data provided is sound, encouraging and this team is in a unique position to develop a technology that will have a tangible impact for patients with PD.
- The microfluidic approach is interesting. The engineering appears solid.
- This approach likely has potential for Parkinson's and other diseases.

Concerns

- There was very little preliminary data demonstrating this approach will work at a useful level, particularly considering the inherent variability in different iPSC lines.
- To this reviewer, the planning to get to a clinical candidate was lacking beyond very superficial attention.
- Pitfalls are not usefully identified.
- The use of GMP reagents introduces an unwarranted expense at such an early stage.
- Aspects related to the heterogeneity of the disease should have been further addressed. This point is also valid when it comes to justifying using solely the DAergic cell phenotype as it may not mitigate some of the most debilitating problems experienced by PD patients (e.g. cognition).
- Problems related to pathological protein transmissibility should have also been discussed.

Application #	DISC2-10085
Title (as written by the applicant)	Stem Cell-based Modeling and Therapeutic Targeting of IDH Mutant Gliomas
Research Objective (as written by the applicant)	Using stem cell and progenitor-based models to repurpose therapeutics that show specificity against IDH1 mutant glioma cells while sparing regenerative cell populations in the adult brain.
Impact (as written by the applicant)	The proposal will generate lacking pre-clinical tools to study IDH1 mutant gliomas and repurpose pharmaceuticals that can readily be implemented in the clinic to improve outcome of patients.
Major Proposed Activities (as written by the applicant)	• High-throughput screening of FDA-approved and clinically relevant compounds to link cell viability with IDH1 mutation status in human gliomas and neural stem/progenitor cells • Use of human iPS-derived neural stem and progenitor cultures to link biological activity to genetic alterations commonly found in subgroups of IDH1 mutant gliomas. • High-throughput screening of bioactive and epigenetic compounds to link cell viability with IDH1 mutation status in human gliomas and neural stem/progenitor cells
Statement of Benefit to California (as written by the applicant)	Glioma is the most common primary malignant brain tumor, where IDH mutant tumors represent approximately 50% of these patients. This pioneering work will use human induced pluripotent stem cells and patient-derived tumor cells to establish pre-clinical models of IDH mutant gliomas that are currently lacking. High-throughput screens of FDA-approved drugs and other compounds represent an accelerated approach to improve outcome in glioma patients and reduce the cost for the State of California.
Funds Requested	$2,192,183
GWG Recommendation	***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 average of the individual member scores. Additional parameters related to the score are shown below.

Mean	77
Median	75
Standard Deviation	9
Highest	90
Lowest	60
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	3
(1-84): Not recommended for funding	12

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	10	1	4
Is the rationale sound?	4	7	4
Is the proposal well planned and designed?	2	6	7
Is the proposal feasible?	3	5	7

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The use of iPSCs to make IDH1 positive neural stem cells and the other mutations is novel.
- Targeting cells with IDH1 mutations before they get other mutations makes sense.

Concerns

- The PDX models are not different than other teams doing the same thing.
- The utility of the iPSC derived model is unclear.
- The prioritization of hits within the screen is not clear.
- The point of going on to the second screen when the outcomes of the first screen is unclear does not make sense.
- The fundamental problem to this reviewer is that by the time a tumor is apparent, whether IDH1 mutations have already transitioned to a passenger stage. This is likely to be particularly problematic in the nervous system. Thus, the transition to the clinic is very unclear, as clinical trials tend to be conducted on advanced malignancies rather than on a primary tumor.
- If IDH1 mutation becomes a passenger at a very early stage in the process of transformation, then the value of this approach becomes very questionable.
- There is a concern that this is an elegant model of something that does not have the potential to move out of the laboratory. This is not well-addressed. If a patient presents with an actual tumor, under what circumstances would targeting an early stage mutation be relevant?
- The Gleevec experience is only partially informative on this, in that Drucker's initial studies were able to show efficacy in early stage tumors. After blast crisis, however, Gleevec efficacy is minimal. A clear case was not made that it is even possible to get to the clinic with an approach that may be limited in its effects to before, and potentially well before, blast crisis.
- The presentation of Aim 2, on generating models of glioma using human cells does not present a convincing argument as to why this is more valuable than the thousands of existing glioma cell lines that have high levels of cancer stem cell representation.

Application #	DISC2-10088
Title (as written by the applicant)	Preclinical development of AAV vector-mediated in vivo hepatic reprogramming of myofibroblasts as a therapy for liver fibrosis
Research Objective (as written by the applicant)	An intravenously injectable virus that converts the scar cells responsible for liver cirrhosis into the cells that provide most of the liver's function, thereby preventing or reversing liver failure.
Impact (as written by the applicant)	The proposed research will develop a new therapy for liver cirrhosis, which can be cured by liver transplantation, but there are not enough donor organs for all patients in need.
Major Proposed Activities (as written by the applicant)	• Construction of a single AAV vector expressing the human transcription factors FOXA3, HNF1A and HNF4A effective in hepatic reprogramming of human myofibroblasts. • Identification of chimeric AAV capsids that transduce human myofibroblasts in vivo with high efficiency and specificity. • Identification of human myofibroblast-targeted chimeric AAV capsids that are not neutralized by human antibodies against naturally occurring AAV capsids. • Demonstration of therapeutic efficacy and principal safety of in vivo hepatic reprogramming of human myofibroblasts.
Statement of Benefit to California (as written by the applicant)	California has one of the longest wait times for a donor liver in the US. Therefore, many Californians with liver cirrhosis have to be hospitalized or die while waiting for a transplant. By developing a broadly applicable new therapy for liver cirrhosis, the proposed research will improve the outcomes of patients with liver cirrhosis and reduce the financial burden on California's medical system.
Funds Requested	$1,638,389
GWG Recommendation	***Exceptional merit and warrants funding, if funds are available***

Scoring Data

Final Score: 91

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

Mean	92
Median	91
Standard Deviation	4
Highest	95
Lowest	85
Count	12
(85-100): Exceptional merit and warrants funding, if funds are available	12
(1-84): Not recommended for funding	0

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	12	0	0
Is the rationale sound?	12	0	0

Is the proposal well planned and designed?	9	2	1
Is the proposal feasible?	9	2	1

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- Remarkable concept.
- A very strong application based on strong preliminary data.
- A very systematic and rational approach.
- An excellent and innovative approach.
- The proposal may provide paradigm-changing advances in liver fibrosis.
- The team is outstanding.

Concerns

- A concern is the efficacy of the three transcription factors to reprogram human cells. The efficacy might not be as strong compared to the mouse.
- The focus is entirely on liver fibrosis. Preclinical models of fibrosis in pancreas, heart (after myocardial infarct), and other common sites of fibrosis in humans should be tested for inappropriate hepatic conversion by the AAV6 vectors under consideration.
- The proof of principle on human MF is very useful. However, these data also show that human MFs are more difficult to reprogram (below 15%) and might react differently to their cocktail of transcription factors. The resulting cells also seem less functional.
- Inflammation plays a key role in the human disease. The CCL4 model is an injury model that does not fully recapitulate this aspect.
- Discussion of potential pitfalls is limited to overcoming technical hurdles.
- Off target effects need to be considered - i.e. reprogramming fibroblasts outside the liver.

Additional Comments

- AAV vector-mediated liver-directed gene therapy targets trans-differentiation of endogenous fibrotic tissue. While this does not utilize stem cell technology, it could augment other approaches that engraft hepatocytes differentiated from stem cells.

Application #	DISC2-10090
Title (as written by the applicant)	Human Cardiac Chip for Assessment of Proarrhythmic Risk
Research Objective (as written by the applicant)	This proposal will develop patient specific 'heart-on-a-chip' devices that will significantly impact early screening of drugs to accurately predict drug-induced proarrhythmia and toxicity.
Impact (as written by the applicant)	Patient specific 'heart-on-a-chip' device will significantly reduce the cost of bringing a new drug candidate to market while improving efficacy.
Major Proposed Activities (as written by the applicant)	• To improve the maturity of human induced pluripotent stem cell derived cardiac myocytes (hiPSC-CM) in the heart chip. • To validate the predictive response of the improved cardiac MPS using drugs with known arrhythmia risk. • To assess the response of drugs with known arrhythmia risk on a cardiac chip with LQT1 hiPSC-CMs. • To develop a Target Product Profile/Product Concept Document for the cardiac MPS.
Statement of Benefit to California (as written by the applicant)	We will create a patient specific 'heart-on-a-chip' device that will have a significant impact on the development of drugs. A major aspect of this proposal is to establish a heart chip assay to accurately predict drug-induced proarrhythmia and toxicity. If successful, we can reduce the cost and time needed to bring new drugs to market, thereby improving the lives of many Californians and significantly reducing the cost to California's healthcare system.
Funds Requested	$944,721
GWG Recommendation	***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 average of the individual member scores. Additional parameters related to the score are shown below.

Mean	90
Median	90
Standard Deviation	3
Highest	95
Lowest	83
Count	11
(85-100): Exceptional merit and warrants funding, if funds are available	10
(1-84): Not recommended for funding	1

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	11	0	0
Is the rationale sound?	10	1	0
Is the proposal well planned and designed?	11	0	0

Is the proposal feasible?	11	0	0

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- Strong preliminary data.
- The proposal is more focused and responsive to comments from previous review.
- 3D model is a major strength.
- A well-focused proposal.
- A good model system.
- Excellent preliminary data, very strong team of investigators, and an area of significant need.

Concerns

- *None indicated*

Application #	DISC2-10092
Title (as written by the applicant)	Nomination of a clinically approved drug that inhibits the Rho kinase pathway for treatment of intellectual disability associated with OPHN1 Syndrome
Research Objective (as written by the applicant)	Use structural modeling and OPHN1 patient iPSCs to rapidly identify and repurpose an approved drug with ROCK1/2 inhibitory properties for a new clinical trial in OPHN1 patients.
Impact (as written by the applicant)	OPHN1 syndrome. Potentially other neurologic, cardiovascular, and pulmonary conditions with heightened ROCK activity. Provides proof of concept for rapid drug repurposing and testing in patient iPSCs.
Major Proposed Activities (as written by the applicant)	• Using advanced artificial intelligence drug prediction methodology, identify ~15 FDA approved drugs predicted to inhibit ROCK (completed) • Test predicted ROCK inhibitors biochemically with in vitro ROCK 1/2 kinase assays to identify those with inhibitory potential. • Develop one additional OPHN1 Intellectual Disability Syndrome patient iPS cell line (two already exist). • Confirm ROCK inhibitory effects in live cells and test for amelioration of OPHN1 disease state in neurons derived from OPHN1 patient iPSCs. • Testing ROCK1/2 inhibitors' ability to rescue the phenotype in vivo in mice lacking OPHN1 • Nominate a candidate for clinical trials in OPHN1 patients.
Statement of Benefit to California (as written by the applicant)	This project will directly benefit Californians affected by OPHN1 syndrome. It may also lead to direct benefit for patients affected by the many other neurologic, pulmonary, and cardiovascular conditions characterized by heightened Rho signaling in which ROCK inhibitors have shown clinical efficacy. Finally, if successful, our research provides a new model for rapid drug repurposing and further validates the artificial intelligence methodology of a California-based company (Atomwise).
Funds Requested	$405,750
GWG Recommendation	***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 average of the individual member scores. Additional parameters related to the score are shown below.

Mean	79
Median	80
Standard Deviation	4
Highest	84
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	11	1	3
Is the rationale sound?	8	3	4
Is the proposal well planned and designed?	1	8	6
Is the proposal feasible?	5	3	7

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths or Concerns

- The main strength of this application is the rationale and strategy proposed to repurpose FDA-approved drugs that target ROCK. This is an elegant method that likely will result in the identification of interesting compounds that could be used for further in vivo studies.
- A major strength of this proposal is that it seems to be patient advocate driven. This is a group of advocates for a particular rare disease who have decided to take things into their own hands and do something about it. This is made possible by the relatively recent commoditization of research and the ability of an individual or group with enough motivation to do cutting edge research.
- Patient advocate group driven research. May be a paradigm for other research.
- Good plausibility - pathway is understood, ROCK inhibitor drugs can be selected. Works in rodents.
- Immediate clinical availability by use of pre-approved drugs.
- The preliminary data provided is promising with evidence that blocking ROCK with Y-27632 inhibitor generates improvements on some behavioral aspects of the disease as well as in cell models in which the treatment reestablishes dendritic spine deficits, for example.
- Overall, there is clearly a basis/justification for investigating the potential of other currently available drugs that can inhibit the ROCK pathway. The preliminary data in cell lines and animal models is encouraging and these types of drugs have already shown tolerability in humans.

Concerns

- The applicants propose to repurpose existing drugs identified by the company's software, which constitutes an interesting and efficient approach. However, in the list of drugs that could be used for the treatment of OPHN1, several of the mentioned drugs have vasodilation (e.g. Pindolol) or anti-adrenergic effects (e.g. Carteolol). This may have an unwanted effect in patients treated primarily for OPHN1 syndrome. The applicants fail to address this important issue.
- The Rho/ROCK pathway is implicated in a large number of vital functions such as cell cycle control, proliferation and cytoskeleton remodeling and stabilization. The applicants do not discuss if inhibiting ROCK could be expected to generate unintended effects.
- The experiments that pertain to drug validation in animal models, which are critical to this work, are too superfluously described/justified.
- Off target effects are not discussed. Sparse preliminary evaluation in cells or animals.
- A key weakness of the application is the proposed experiments (electrophysiology, neuronal morphology, synapse staining) that will be used to assess the effectiveness of the compounds on iPSC derived neurons. All these parameters are probably very variable already amongst control cell lines. It is unclear which control lines will be used and no z-score is provided for the proposed phenotypes.
- The timeline proposed to perform all the electrophysiological experiment (3 months) is just not realistic at all. It is then ultimately unclear which phenotype the researchers will use as their ultimate readout. Choosing a clear set of phenotypes that are most relevant to the human disease would be helpful.
- The strategy to move from iPSC studies to animal studies is not well-described.
- The proposed concentration and timing of the drug delivery to the iPSC-derived neurons is not provided. Potential pitfalls are not discussed.
- The proposal needs to discuss the potential of the compounds to have side effects, controls for each experiment, readouts for each experiment, and detail the mouse work.
- It would be helpful to pre-identify the CRO.

- May be too ambitious in terms of time and/or budget. Consider scaling back the scope (e.g., by eliminating the mouse work). Could be done in a future grant.
- Some proposed work appears to be already done in preliminary data. Need clarification of the work that will be done in future.

Additional Comments

- Reviewers would like to see a revision of this proposal.
- Applicants might consider providing information on how representative the OPHN1 advocacy group is of the OPHN1 community. e.g., other competing advocacy groups, number of members.

Application #	DISC2-10093
Title (as written by the applicant)	Human iPSC-based phenotypic screening tool development for drug identification in Parkinson's disease
Research Objective (as written by the applicant)	Development of a human-derived stem cell-based technology for screening and drug development in Parkinson's disease.
Impact (as written by the applicant)	The human stem cell-based technology should improve the likelihood of therapeutic entities for neuroprotection reaching the market for people with Parkinson's and other neurodegenerative diseases.
Major Proposed Activities (as written by the applicant)	• Assay optimization in human iPSC-derived neuronal cultures to assess general cell toxicity. • Assay optimization in human iPSC-derived neuronal cultures to assess mitochondrial function. • Assay optimization in human iPSC-derived neuronal cultures to assess protein clearance pathways. • Assay optimization in human iPSC-derived neuronal cultures to assess Parkinson's specific protein changes and accumulation. • Validate the technology using drug like compounds that are known to have a high-safety profile and could move forward to clinical studies. • Develop a product concept document and identify commercial partners to license the technology to develop new treatments.
Statement of Benefit to California (as written by the applicant)	Estimated 36,000-60,000 people in California are affected with Parkinson's disease (PD) which is a neurodegenerative disease that causes a high degree of disability and financial burden for our health care system. This project will provide substantial benefits to California and its citizens by developing new PD-relevant human stem cell-derived culture model that can distinguish the appropriateness of new therapeutics for drug development with the ultimate goal of advancing into clinical trials.
Funds Requested	$1,191,960
GWG Recommendation	***Not recommended for funding***

Scoring Data

Final Score: 71

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

Mean	72
Median	71
Standard Deviation	2
Highest	75
Lowest	70
Count	12
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	12

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	9	0	3
Is the rationale sound?	1	6	5
Is the proposal well planned and designed?	0	9	3
Is the proposal feasible?	0	5	7

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- If successful, the technology could identify promising PD compounds for further *in vivo* testing.
- If successful, a platform for screening PD drugs would be useful.

Concerns

- The complexity of the platform may make it an imperfect screening tool.
- Limited impact because only screening lines with rare PD associated mutations. It is unclear if this the right target to be screening drugs.
- No *in vivo* testing is proposed.
- The rationale is not new and numerous studies using iPSCs for *in vitro* drug screens have been attempted. The selected compounds have likely been tested already. It is not clear if this application will be more successful.
- Some readout assays are based on fluorescence staining and may not be sufficient to make certain conclusions.
- The basic science is sound, but the response of isolated iPSCs may not mirror the response of patients.
- Scant attention is paid to strategic pitfalls and alternatives.
- No publications reported by PI to date on 3 prior CIRM grants.
- IPSC modeling will exclusively be developed in cell lines derived from genetic forms of the disease, including the rare LRRK2 mutation. Despite the fact that the applicants mention having cell lines from sporadic cases, they are not planning to develop/test the assays in them.
- It is unclear how iPSC modeling would better translate screened drugs to the clinic, especially given that the cell lines only account for less than 10% of PD cases.
- It should have been within the scope of this proposal to evaluate safety of identified compounds in *in vivo* systems.
- The applicants do not discuss their strategy if one or more of their compounds fail in one or more test panels.

Application #	DISC2-10099
Title (as written by the applicant)	Towards hepatocyte cell replacement therapy: developing a renewable source of human hepatocytes from pluripotent stem cells
Research Objective (as written by the applicant)	To develop a consistent and abundant source of transplantable human hepatocytes for transplantation
Impact (as written by the applicant)	Developing an abundant and consistent source of human hepatocytes that can be used to treat patients with liver failure
Major Proposed Activities (as written by the applicant)	• To profile cell-type specific surface markers expressed on hPSCs and hPSC-derived hepatocytes • To purify hPSC-derived liver progenitors and hepatocytes and eliminate risk of residual pluripotent population • To track long-term localization and cell-growth of transplanted hPSC-derived hepatocytes after transplantation into injured mouse livers • To determine the degree by which hPSC-derived hepatocytes engraft and functionally restore liver function in various mouse models of severe liver injury • To assess long-term safety of transplanted hepatocytes in vivo
Statement of Benefit to California (as written by the applicant)	Liver failure is one of the 12 leading causes of adult death in the U.S. The only long-term treatment for liver failure is to transplant a new liver, but there is a grim shortage in available livers, with many patients dying while awaiting a suitable liver. Our research aims to generate large numbers of human liver cells derived from stem cells that could one day be used to treat patients with liver disease and end-stage liver failure.
Funds Requested	$2,201,136
GWG Recommendation	***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 average of the individual member scores. Additional parameters related to the score are shown below.

Mean	80
Median	80
Standard Deviation	7
Highest	93
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	6
(1-84): Not recommended for funding	9

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion

influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	12	1	2
Is the rationale sound?	8	3	4
Is the proposal well planned and designed?	1	7	7
Is the proposal feasible?	2	8	5

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- hPSC differentiation protocols produce hepatic progenitors and stable cells that express hepatocyte markers that are functional *in vivo*.
- The applicants can test if engraftment of liver progenitor cells prolongs survival and ultimately restores more liver function, over a longer time period, compared to transplantation of mature hepatocytes or other treatments. Perhaps engraftment of a combination of mature and progenitor cells is best for both short-term benefit and long-term survival.
- Liver diseases are a major health problem and the development of a new therapy is urgently needed.
- The combination of animal models for testing hPSC-derived hepatocytes is very powerful and interesting.

Concerns

- Several aspects of the proposal are not realistic in the context of future clinical applications including FACS sorting cells for transplantation and the use of MET for increasing engraftment.
- Expertise in animal models appears limited.
- Caveats in Fig 7b: total bilirubin is reduced after engraftment but the FRG mice tested do not even appear to be jaundice. Yellowing of the eyes and skin starts to be noticeable at levels of about 2 to 3 mg/dl, whereas FRG mice tested were in the high normal range at 1.5 mg/dL. Efficacy in extreme cases should be tested.
- Aim 2.1 proposes an important extension of the data in Fig 7b showing a 2-fold survival benefit to FRG mice engrafted with hPSC-derived hepatocytes over 40 days. This is a short-term benefit and it is unclear what is the survival benefit over many months in FRG mice. Human patients need years of survival benefit.
- Requisite sorting for cell population identification combined with establishing new animal models underestimates the time required to complete milestones.
- Liver gene expression is compared to media vs human hepatocytes coupled with lack of statistical data on survival reduces enthusiasm.
- FACS sorting likely means that very few cells will be available for transplantation.
- Concerns were raised regarding the animal models and the proposed timeline.

Application #	DISC2-10107
Title (as written by the applicant)	A Novel Approach to Eradicate Cancer Stem Cells
Research Objective (as written by the applicant)	The outcome is a therapeutic candidate ready for Investigational New Drug (IND)-enabling studies to target a central hub of stemness pathways of cancer stem cells (CSC) maintenance and self-renewal
Impact (as written by the applicant)	To date, the majority of metastatic cancers remain incurable, because CSCs that can grow new tumors evades current therapy. The proposed studies aim to eradicate CSCs to achieve a cure.
Major Proposed Activities (as written by the applicant)	• Investigate the effects of therapeutic candidates on colorectal CSCs in cellular and patient-derived xenograft (PDX) models • Confirm the direct effects of candidate therapeutics in isolated colorectal CSCs and compare the effects with other experimental agents that inhibit other pathways that affect CSCs • Define the mechanism of how candidate therapeutics inhibit CSCs • Continue to fine tune candidate therapeutics to improve specificity and potency and address issues of the current lead compounds by medicinal chemistry • Investigate toxicity, eliminate toxic compounds, and define the safety profile of the lead candidate therapeutics • Identify the optimal candidate for IND-enabling studies and define target product profile
Statement of Benefit to California (as written by the applicant)	According to the California Cancer Registry, more than 19 million Californians are at risk for cancer, and nearly 800,000 are living with active cancer. To date, the majority of metastatic cancers remain incurable. Metastasis is driven by cancer stem cells (CSCs), which are resistant to currently available treatments. We will develop an effective new drug that targets and eradicates CSCs, to ultimately increase the cancer cure rate, reduce medical costs, and improve outcomes for Californians.
Funds Requested	$1,839,484
GWG Recommendation	***Exceptional merit and warrants funding, if funds are available***

Scoring Data

Final Score: 84

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

Mean	76
Median	84
Standard Deviation	16
Highest	92
Lowest	50
Count	12
(85-100): Exceptional merit and warrants funding, if funds are available	6
(1-84): Not recommended for funding	6

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	9	2	1
Is the rationale sound?	6	3	3
Is the proposal well planned and designed?	3	4	5
Is the proposal feasible?	5	3	4

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The compound is novel.
- The approach is a functional rather than phenotypic assessment of CSCs.
- The investigative team is well-suited to carry out the proposed studies.
- Testing human PDX is a critical component of the application.
- The goal of this project is to develop a specific and potent sumoylation inhibitor that could be added to the armamentarium of chemotherapy agents for colorectal cancer. Colorectal cancer has a major morbidity/mortality impact. Even if this therapy ends up only being applicable for a small percentage of CRC, or has only a minor effect on CRC, it could have an overall large public health benefit.

Concerns

- The claim that the applicants will be testing this drug against cancer stem cells is not substantiated as they are using cell lines.
- The details for how this molecule will inhibit sumoylation and CSC survival were missing.
- The toxicity of the drug on normal cells was not well-addressed.
- Eradicating cancer by inhibiting a fundamental pathway such as sumoylation is interesting but not novel.
- Groups have being trying for ~5 years to develop sumoylation therapies for cancer, and to date, none have made it through clinical trials. So it is possible that this is a dead end. However, the current proposal claims to have a better inhibitor, so it is worth a try.
- The project could probably be done without using isolated CSC, i.e., by skipping Milestone 2, but it is reasonable to use the CSC.

Application #	DISC2-10108
Title (as written by the applicant)	ADAR1 Enhanced Expansion of Self-renewing Human Hematopoietic Stem Cells
Research Objective (as written by the applicant)	We will develop an efficient ex vivo cord blood HSC expansion strategy by reprogramming of ADAR1-mediated self-renewal transcripts and MBNL3 knockdown in a stem cell bioreactor expansion platform.
Impact (as written by the applicant)	This will overcome the low HSC number collected from placenta and provide vital clinical uses including regenerative medicine and bone marrow transplantation for a variety of hematologic malignancies.
Major Proposed Activities (as written by the applicant)	• RNA editing activity will be elucidated using whole transcriptome sequencing, RESS-qPCR, and RNA editing reporter activity in FACS-purified cord blood HSCs. • The capacity of ADAR1 WT and mutant ADAR1E912A to enhance cord blood HSC self-renewal will be determined in stromal co-cultures and following transplantation of RAG2-/-gc-/- mice. • The capacity of ADAR1 WT to alter HSC cell cycle transit will be determined in stromal co-culture and in humanized RAG2-/-gc-/- mice using our FUCCI2BL imaging system and FACS analysis. • The capacity of ADAR1 WT to edit MBNL3 transcripts and enhance HSC survival/self-renewal will be determined using RESSqPCR, stromal co-cultures, replating assays and mice transplantation. • The capacity of MBNL3 shRNA knockdown to enhance HSC survival and self-renewal will be quantified in human stromal co-cultures, replating assays and by transplantation of RAG2-/-gc-/- mice. • The capacity of lentiviral ADAR1 WT and lentiviral MBNL3 shRNA knockdown to enhance cord blood HSC expansion ex vivo will be compared using an established clinical bioreactor system.
Statement of Benefit to California (as written by the applicant)	Unrelated donor umbilical cord blood (CB) is a key source of hematopoietic stem cells (HSCs) for allogeneic transplantation. However, limited number of HSCs has precluded CB transplantation in most adults. Successful ex vivo expansion of CB HSCs would enhance curative options for patients with refractory hematologic malignancies and accelerate stem cell gene therapy approaches for devastating degenerative disorders resulting in a major positive therapeutic and economic impact for Californians.
Funds Requested	$2,167,200
GWG Recommendation	***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 average 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

Score Influences
Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	4	5	4
Is the rationale sound?	2	7	4
Is the proposal well planned and designed?	0	10	3
Is the proposal feasible?	0	8	5

Reviewer Comments
The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths
- *None indicated*

Concerns
- The proposal is descriptive and the vast majority of the studies are non-informative vis-a-vis the ultimate goal of the project.
- The benefits of the strategy compared to other approaches is not apparent.
- The benefits of the strategy are poorly described and not convincing.
- Modest expansion is shown in preliminary data.
- The proposal lacks focus.
- Experimental plan is highly descriptive and, by the end, no true validation of strategy will be performed.
- Modest preliminary data.

Application #	DISC2-10110
Title (as written by the applicant)	Multipotent Cardiovascular Progenitor Regeneration of the Myocardium after MI
Research Objective (as written by the applicant)	We developed technology to reproducibly prepare large numbers of bonafide cardiac progenitor cells from patient iPSCs. We propose the first test of these cells as a therapy for myocardial infarction.
Impact (as written by the applicant)	Heart failure resulting from myocardial infarction is responsible for 13% of human mortality (WHO statistic). This proposed therapy is to restore the loss of heart cells that lead to heart failure.
Major Proposed Activities (as written by the applicant)	• Perform cell labeling, biobanking and in vitro characterization of Multipotent Cardiovascular Progenitor cells (MCPs), including quality control of batches for subsequent activities. • Phase 1: Deliver the Multipotent Cardiovascular Progenitor cells (MCPs) into pig hearts after infarction/reperfusion. Use 19F magnetic resonance imaging (MRI) to measure retention and distribution. • Phase 2: Using the conditions determined in Phase 1, monitor animals for 3 months to assess safety & efficacy for improving heart function & survival. Histology at termination to assess regeneration. • Summarize the results into a preclinical package, in anticipation of translating the research into a cell-based therapy for myocardial infarction
Statement of Benefit to California (as written by the applicant)	Heart disease accounts for 25% of deaths in California, making it the #1 cause of death (2014, American Heart Association). Over 3% of Californians have had a heart attack, but with 60% obesity this number will likely increase. The research investigates a curative therapy based on cell transplantation of bonafide cardiac progenitors. Benefits likely to accrue therefore are 1) improved health of our population, and 2) stimulation of biotechnology to produce, market and deliver the therapeutic.
Funds Requested	$1,817,654
GWG Recommendation	***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 average of the individual member scores. Additional parameters related to the score are shown below.

Mean	92
Median	90
Standard Deviation	3
Highest	95
Lowest	90
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	0

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	12	0	1
Is the rationale sound?	12	0	1
Is the proposal well planned and designed?	11	1	1
Is the proposal feasible?	12	0	1

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The proposal presents strong preliminary data.
- A very detailed description of experiments is provided, including detailed phenotyping.
- Identification of the MCPs is rigorous with the Tinman phenotype.
- Monitoring of the live cells in the heart is a real strength.
- A CHF cell product is an unmet clinical need.
- Outstanding investigator and environment, solid rationale, and high quality preliminary data.

Concerns

- A concern that too few animals will be tested.
- The number of pigs that they will use seems small and may make it hard to make conclusions.

Application #	DISC2-10120
Title (as written by the applicant)	Microenvironment for hiPSC-derived pacemaking cardiomyocytes
Research Objective (as written by the applicant)	This proposal investigates the effects of the microenvironment on the development and maintenance of pacemaking function in human induced pluripotent stem cell (hiPSC)-derived cardiomyocytes.
Impact (as written by the applicant)	Pacemaking function of hiPSC-derived cardiomyocytes is lost over time. Sustainability of pacemaking function of these cells is critical for engineering an biopacemaker from the patient's own cells.
Major Proposed Activities (as written by the applicant)	• Determine the effects of matrix scaffolds on the differentiation and maintenance of pacemaking function in hiPSC-derived cardiomyocytes. • Determine the appropriate hiPSC-derived cardiac cells to be subjected to the microenvironment for efficient yield of pacemaking hiPSC-derived cardiomyocytes. • Induce vascularization in tissue constructs in small animals to sustain pacemaking tissue construct. • Test sustainability of a functional pacemaking tissue construct in a small animal model.
Statement of Benefit to California (as written by the applicant)	Over 350,000 patients a year in the U.S. require an electronic pacemaker to restore their heart rhythm. The annual healthcare burden amounts to $20 billion. Repeated surgeries to replace battery and electrical parts generate additional costs and suffering for the patients. A biopacemaker engineered from human stem cell-derived pacemaking cells can overcome problems associated with electronics and improve the quality of life for the pacemaker recipient while reducing cumulative health care costs.
Funds Requested	$2,042,728
GWG Recommendation	***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 average of the individual member scores. Additional parameters related to the score are shown below.

Mean	89
Median	90
Standard Deviation	2
Highest	90
Lowest	84
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	12
(1-84): Not recommended for funding	1

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	12	1	0
Is the rationale sound?	11	0	2
Is the proposal well planned and designed?	11	0	2
Is the proposal feasible?	12	0	1

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- If successful, the technology could provide iPSC-based pacemakers that can be used for further *in vivo* tests.
- Enthusiasm for focusing on patients who would most benefit, neonates and aged who face repeated MRI, as pacemakers are effective for most others.
- Strong rationale.
- Good preliminary data.
- This is an excellent resubmission where the PI is planning on devising a biological pacemaker using human iPSC-derived myocytes in conjunction with porcine ECM scaffold. The translatability and the likelihood of success is high.
- The use of biomimetic ECM is highly innovative.

Concerns

- It is unlikely that this approach will be a cost effective considering expenses required to manufacture these pacemakers for each patient.
- Use of iPSCs as opposed to more cost-effective immunomatched ESCs is not well justified.

Application #	DISC2-10124
Title (as written by the applicant)	Targeted Gene Editing in the Treatment of X-Linked Hyper-IgM Syndrome
Research Objective (as written by the applicant)	We are seeking to develop site-specific hematopoietic stem cell gene therapy with autologous transplant as a definitive treatment option for X-linked Hyper-IgM Syndrome.
Impact (as written by the applicant)	These studies would bring stem cell gene therapy for X-HIGM closer to the clinic, as there are currently no options for those without an HLA match or with infections too severe for allogeneic HSCT.
Major Proposed Activities (as written by the applicant)	• Identify the optimal CRISPR gRNA, Cas9 variant, and cDNA donor template targeting the CD40L gene. • Compare TALENs and CRISPR/Cas9 targeting the CD40L gene in terms of their activity, specificity, and ability to allow homology-directed repair in CD34+ PBSC through short term cultures in vitro. • Evaluate methods to maximize gene editing and maintain HSC survival and pluripotency. • Evaluate the efficacy of optimized genome-editing reagents in hematopoietic stem cells long term in vitro in the artificial thymic organoid system and in vivo in NSG mice. • Assess gene editing of the CD40L gene of X-HIGM patient derived CD34+ cells using the optimal gene editing platform and reagents determined in Milestones 1-4.
Statement of Benefit to California (as written by the applicant)	Safe, definitive therapies for X-HIGM represent an unmet medical need. Allogeneic stem cell transplant is frequently complicated by graft-versus-host disease and worsening of pre-existing infections. Successful demonstration that stem cell gene therapy can safely and effectively cure X-HIGM will shift the paradigm by which patients will be treated, led by California's position as a leader in the field of gene therapy. This will result in improved patient care in the state and around the world.
Funds Requested	$1,665,908
GWG Recommendation	***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 average of the individual member scores. Additional parameters related to the score are shown below.

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

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	15	0	0
Is the rationale sound?	15	0	0
Is the proposal well planned and designed?	15	0	0
Is the proposal feasible?	15	0	0

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- Excellent revised application.
- The design, team and models proposed are excellent.

Concerns

- *None indicated*

Application #	DISC2-10129
Title (as written by the applicant)	Non-Toxic, Highly-Effective Bioinspired Cryoprotectants for On-Demand Stem Cell Therapies
Research Objective (as written by the applicant)	An advanced technology is sought to replace the toxic, ineffective and highly processed components in legacy cryopreservation media. This technology is a fundamentally novel non-toxic freezing media.
Impact (as written by the applicant)	The transport and storage of stem cell therapies is crippled by freezing media with poor cell preservation. Significantly improved freezing media would directly increase therapy success rate.
Major Proposed Activities (as written by the applicant)	• Human pluripotent stem cells will be cryopreserved using groundwork proof-of-concept cryopreservation formulas and cells will be evaluated for cytotoxicty and survival by post-thaw analysis. • Bioinspired polymers with ice-inhibiting properties will be synthesized and optimized for inclusion into a new freezing media. • Freezing media formula and methods-of-use will be further developed (from Activity 1) to freeze and thaw a model stem cell system yielding ultra-high cell survival and viability. • Human induced pluripotent stem cells will be cryopreserved using advanced freezing media. Survival and phenotype of differentiated cells will be compared to non-frozen and DMSO-preserved cells. • A functional analysis of cryopreserved differentiated cells will be completed using secondary screened freezing media and methods-of-use with comparison to non-frozen and DMSO-preserved cells. • Scale-up for a translational application. The formula will be selected from Activity 3/4/5 and the freeze media will be scaled in preparation for work with an industrial cell manufacturer.
Statement of Benefit to California (as written by the applicant)	California is home to the world's most cutting-edge stem cell research to advance biomedical therapies and improve the quality of life for those suffering from a wide variety of diseases. Yet, the infrastructure to safely deliver on-demand cell therapeutics is lagging behind. This proposal supports a critical value to Californians: calm and comfort from knowing their therapy can be stored, transported and delivered safely to their bedside in a time of need, with maximum therapeutic efficacy.
Funds Requested	$887,883
GWG Recommendation	***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 average of the individual member scores. Additional parameters related to the score are shown below.

Mean	82
Median	85
Standard Deviation	7
Highest	90
Lowest	60
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	8
(1-84): Not recommended for funding	7

Score Influences
Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	13	0	2
Is the rationale sound?	9	3	3
Is the proposal well planned and designed?	5	4	6
Is the proposal feasible?	5	2	8

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- Outstanding potential for all stem cell transplantation therapies.
- The focus on a naturally occurring antifreeze protein is a plus.
- Elegant experimental design and methods to measure ice formation.
- The need for improved cryopreservation is very real. Thus, the approach is on an important topic.
- This is a strong proposal that is focused on developing novel synthetic peptoids for the plain purpose of enhancing cell survival following freezing. The strength of the proposal lies in the preliminary data and the technology platform that has been developed, and the high likelihood of success.

Concerns

- The proposal does not focus on cells which are used for cell therapy. Various cells are likely to show different behavior.
- The approach needs to be tested in preliminary experiments on primary cells, both progenitor cells and terminally differentiated cells ready for transplantation. If it works, this would greatly increase enthusiasm.
- One drawback is that the investigators did not disclose any details about their compounds or the mechanism by which these compounds work.
- Applicants should test varied types of stem cells.
- Needs more proof of principle data with stem cells.
- The applicants did a freeze and thaw on cardiomyocytes with DMSO and use this data to show they need something better, but unfortunately did not perform the key experiment to demonstrate better recovery of cardiomyocytes. This is such a glaring omission that it raises concerns that either they are not thinking clearly, or that the experiment was done and it didn't work.
- The very restricted focus on cardiomyocytes is also a concern, as different cell types have very different recoveries from freeze and thaw.

Application #	DISC2-10134
Title (as written by the applicant)	Platform Technology for Pluripotent Stem Cell-Derived T cell Immunotherapy
Research Objective (as written by the applicant)	We will combine a novel method to produce T cells from stem cells with gene editing tools, to create pluripotent stem cells that can serve as a universal source of T cells for cancer immunotherapy.
Impact (as written by the applicant)	We will address a major bottleneck for T cell immunotherapy: the complexity and therefore limited access to therapies that must be engineered de novo for each patient.
Major Proposed Activities (as written by the applicant)	• We will design and optimize methods for deletion of 3 key genes that are involved in how T cells respond to, and reject, foreign cells. • We will delete each of the 3 genes separately in pluripotent stem cells (PSCs), and test how each modification affects how T cells develop and function • We will combine deletion of all three genes in the same PSC clone, and test whether we can direct the gene edited T cells to specifically target and kill tumors. • Using our novel method to generate T cells from stem cells, we will thoroughly characterize the gene expression profile in T cells produced from gene-edited PSC.
Statement of Benefit to California (as written by the applicant)	It is estimated that each year over 170,000 Californians will be diagnosed with cancer and approximately 60,000 will die of this disease. Exciting successes have been seen by harnessing the immune system to kill cancer using T cell therapy. However, not all patients who could benefit are able to access this therapy because of the need to manufacture each product from the patients' own blood. An off-the-shelf universal T cell product would dramatically expand the reach of this promising therapy.
Funds Requested	$1,062,076
GWG Recommendation	***Not recommended for funding***
CIRM Recommendation	***Recommended for funding***

Scoring Data

Final Score: 84

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

Mean	83
Median	84
Standard Deviation	3
Highest	86
Lowest	75
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	3
(1-84): Not recommended for funding	12

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	9	1	5
Is the rationale sound?	9	4	2
Is the proposal well planned and designed?	8	4	3
Is the proposal feasible?	4	4	7

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- Artificial Thymic Organoids from stem cells modified to be RAG and B2M deficient is very interesting technology and main strength of proposal.
- This is a high risk, high reward application.

Concerns

- This is a complicated technology that has a low chance of being a cell therapy for many years, if at all.
- Pitfalls were not thoroughly addressed - in fact, the cells will still be antigenic.
- There is concern about possible tumorigenic effects that were not considered or tested.
- Applicants may have insufficient time to complete the proposed study.
- It is unclear if there is a real clinical application.

Application #	DISC2-10142
Title (as written by the applicant)	Development of PEG-PTN for Hematopoietic Regeneration
Research Objective (as written by the applicant)	We will develop a stable form of hematopoietic stem cell growth factor for clinical application.
Impact (as written by the applicant)	Hematopoietic recovery will be improved in myelosuppressed chemotherapy patients.
Major Proposed Activities (as written by the applicant)	• Generation and validation of PEGylated growth factor. • Complete pharmacokinetic analysis of PEGylated growth factor. • Demonstrate effectiveness of PEG growth factor in radiation injury model. • Demonstrate effectiveness of PEG growth factor in bone marrow transplant model. • Demonstrate effectiveness of PEG growth factor in chemotherapy model. • Conduct murine toxicology studies to determine the potential for human drug toxicity and adverse effects.
Statement of Benefit to California (as written by the applicant)	A common life-threatening side effect of chemotherapy treatment is neutropenia accompanied by fever or febrile neutropenia. Patient morbidity, recovery time, and hospitalization in this patient population could be reduced by the addition of this hematopoietic stem cell growth factor to standard treatment regimens.
Funds Requested	$951,920
GWG Recommendation	***Not recommended for funding***

Scoring Data

Final Score: 83

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

Mean	82
Median	83
Standard Deviation	5
Highest	90
Lowest	75
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	7
(1-84): Not recommended for funding	8

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	10	2	3
Is the rationale sound?	6	5	4

Is the proposal well planned and designed?	1	4	10
Is the proposal feasible?	6	2	7

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- Excellent product development.

Concerns

- The results obtained with PEG-PTN were mild.
- The only potential effect was the combination with GCSF but it was not proposed for further testing.
- Effectiveness of drug was not convincing.
- The rationale for why the studies are done in the absence of GCSF, but the preliminary data and goals were to study it in the presence of GCSF was not clear.
- Figure 5 was of concern regarding efficacy and the role of GCSF. There is no difference between GCSF alone and GCSF + PTN.
- The dose response curve could be better defined by route; table is confusing.
- Lab seems to have limited resources.
- There appears to be a low level of support for the PI by the university.

Application #	DISC2-10161
Title (as written by the applicant)	Preclinical testing of retinal tissue from clinical-grade human embryonic stem cells for vision improvement in Rdy/+ cats with retinal degeneration
Research Objective (as written by the applicant)	Retinal tissue patch to treat blindness. We will generate 3D retinal tissue from hESCs, graft into subretinal space of cats with retinal degeneration, demonstrate vision improvement after 6-12 months
Impact (as written by the applicant)	Blindness, caused by various types of retinal degeneration. Primary target (disease): Retinitis Pigmentosa, an orphan class disease with fast track FDA approval; also age-related macular degeneration
Major Proposed Activities (as written by the applicant)	• Aim 1: Optimize hESC-3D retinal tissue derivation from current Good Manufacturing Practice (cGMP)-grade hESCs, characterize our product using FDA criteria for gene and cell therapy products (0-8 mo). • Aim 2: Graft hESC-3D retinal tissue in subretinal space of Rdy/+ cats (8 weeks of age), evaluate vision improvement (behavioral test), structural, synaptic, tumor-free integration of grafts (6-24mo).
Statement of Benefit to California (as written by the applicant)	According to the National Federation of the Blind (2014 Annual Report) 790,700 people in California have blindness or severe visual disability. Grafting hESC-derived retinal patch is the most promising approach to repair vision when photoreceptors degenerate completely. Blindness is both expensive and very debilitating condition to have. Providing a completely blind person the ability to see light again will make a huge positive impact. Our product already enabled a blind animal to see again.
Funds Requested	$1,283,199
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 average of the individual member scores. Additional parameters related to the score are shown below.

Mean	67
Median	65
Standard Deviation	7
Highest	80
Lowest	55
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	9	5	1
Is the rationale sound?	1	13	1
Is the proposal well planned and designed?	0	13	2

Is the proposal feasible?	0	11	4

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The rationale for *in vivo* studies is sound.

Additional Comments

- The grant proposal is poorly assembled.
- Preliminary data on retinal cells is not strong. Not convincing that the cells are high quality.
- Preliminary data from rat experiments is questionable.
- Description and justification of *in vitro* studies are inadequate.
- Potential pitfalls and alternative approaches are not identified.
- Proof that the retinal organoid tissue generated by this group is the best tissue for transplantation is lacking.
- Insufficient time has been given to complete the study.
- The difficulty of the retinal surgery has not been adequately addressed.

Application #	DISC2-10162
Title (as written by the applicant)	Development of Vasculature from iPSCs
Research Objective (as written by the applicant)	The endothelial and smooth muscle lineage cells will be derived from human induced pluripotent stem cells to reconstitute vasculature and restore blood perfusion in ischemic tissues.
Impact (as written by the applicant)	Critical limb ischemia represents a significant unmet medical need without any effective medical therapies for patients at high risk of amputation and may be alleviated by hiPSC-based cell therapy.
Major Proposed Activities (as written by the applicant)	• Determine the optimal stage of hiPSC-derived endothelial progenitor cells for the formation of vasculature in vivo. • Investigate whether the combination of hiPSC-derived endothelial and smooth muscle progenitor cells leads to the formation of more advanced vascular network in vivo. • Enhance engraftment of the hiPSC-ECs in hind limb ischemia (HLI) adult mouse model using a specific survival factor cocktail. • Evaluate the therapeutic effects of the hiPSC-derived vascular lineage cells on restoring blood flow in the ischemic limb of the hindlimb ischemia mouse model.
Statement of Benefit to California (as written by the applicant)	Critical limb ischemia (CLI) is a severe peripheral vascular disease with high risk of amputation, high morbidity and mortality. The annual costs of the treatment of CLI are estimated to be more than $4 billion in the USA. Many CLI patients are not suitable for angioplasties or surgical treatment. Therefore, there is a significant unmet medical need to develop new therapies for CLI. We proposed to develop a novel hiPSC-based cell therapy to treat CLI. Patients in California will be benefited.
Funds Requested	$2,141,519
GWG Recommendation	***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 average of the individual member scores. Additional parameters related to the score are shown below.

Mean	81
Median	80
Standard Deviation	2
Highest	85
Lowest	80
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	1
(1-84): Not recommended for funding	14

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	11	0	4

Is the rationale sound?	8	3	4
Is the proposal well planned and designed?	0	8	7
Is the proposal feasible?	5	1	9

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- An important application based on strong preliminary data.
- The cell survival cocktail used looks promising.

Concerns

- The project is interesting but there are issues with experimental design. Experiments should be done in the relevant mouse model, not in the neonate considering the disease studied affects the adult population.
- The animal model selected is not optimal.
- Project would not result in a huge advance on preliminary data.
- A key concern is the absence of effect in adult mice.
- Combination of several cell types with the addition of growth factors would be challenging to transfer to the clinic.
- Proposed milestones are very similar to what was shown in preliminary data. Major difference is the use of marked cells.
- Many of the experiments repeat what is shown in the preliminary data, but use different cell lines.
- The team could jump to milestone 4 (Evaluate the therapeutic effects of the hiPSC derived vascular lineage cells on restoring blood perfusion in the ischemic limb of the HLI adult mice) in year 1 using cells characterized in their preliminary data.
- Could be done faster than what is described.
- Huge budget request of >$2M ($1M/year). All animals are being bought individually (not bred). Budget should be decreased. The repetitive nature of the some of the experiments should be removed.

Application #	DISC2-10176
Title (as written by the applicant)	Bioprinting A Patch for Cardiovascular Repair
Research Objective (as written by the applicant)	Our candidate cell therapeutic is a cloned early cardiovascular stem cell identified in human neonates that we will 3D bioprint to test regeneration and retention as a patch for cardiac repair.
Impact (as written by the applicant)	Lack of regeneration and limited stem cell retention would be addressed and the outcome would benefit neonatal patients with congenital defects and adults with cardiovascular damage.
Major Proposed Activities (as written by the applicant)	• Bioprint scaffold-free stem cell patches for cardiac transplantation. • Assess the impact of human mesendodermal cardiovascular stem cells on post-infarct repair after intramyocardial injection. • Transplant bioprinted patches and compare stem cell-mediated regeneration after patch placement vs. direct injection of mesendodermal stem cell clones. • Immunostaining to quantify infiltration of host-derived stem cells after cardiovascular stem cell patch placement vs. direct injection in a sheep model of myocardial infarction. • Determine whether or not the non-canonical Wnt signaling pathway is induced during cardiovascular regeneration and repair in this model. • Finalize functional outcome and quantitative analysis and compare outcome upon completion of data collection in all groups.
Statement of Benefit to California (as written by the applicant)	The current costs of annual health care for California residents with heart disease exceed $12,900 per capita, over five times the health care costs of the general adult population. Heart disease affects people of all ages. Congenital heart defects occur in 1% of newborns and 25% of them require surgery. Stem-based therapies such as those we propose here would benefit long term patient outcome, improve the quality of life and reduce medical care costs for people of all ages in California.
Funds Requested	$1,831,499
GWG Recommendation	***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 average 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

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion

influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	3	11	1
Is the rationale sound?	1	13	1
Is the proposal well planned and designed?	1	12	2
Is the proposal feasible?	1	11	3

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- *None indicated*

Concerns

- The statistical plan is inadequate.
- Preliminary data is insufficient.
- The project does not use actual stem cells.
- Lack of convincing preliminary data.
- There are numerous problems with study design.
- Major concerns with statistical analysis.
- This proposal has numerous weaknesses including rationale, type of cells used, source of cells, applicability to human disease, and preliminary data.

Application #	DISC2-10182
Title (as written by the applicant)	Discovery of therapeutics for Huntington's Disease
Research Objective (as written by the applicant)	The objective of the proposed research is to perform 3 independent hESC-based screens to identify drug candidates for Huntington's Disease.
Impact (as written by the applicant)	There are currently no effective treatments for HD. Combination of human isogenic HD-mutants, novel tools and technology will provide therapeutic solutions for this neurodegenerative orphan disease.
Major Proposed Activities (as written by the applicant)	• Screening of 2,000 natural compounds for hits that can rescue the HD germ layer phenotypic signature. • Screening of 2,000 natural compounds for hits that can rescue the HD early neuronal phenotypic signature. • Screening of 2,000 natural compounds for hits that can rescue the HD 'giant multinucleated neurons' phenotypic signature. • In vitro estimation of the potency and toxicity of the top 10 candidate compounds. • In vivo pharmacokinetics studies of the top 5 candidate compounds. • In vivo validation of candidate compounds in an HD mouse model.
Statement of Benefit to California (as written by the applicant)	There are two main benefits for California: First, we will introduce a technology, which does not yet exist outside of my laboratory. This complements the mission of CIRM. Because our platform has a wider application than just modeling HD phenotypes, we anticipate the creation of new industries using these methods. Secondly, an estimated 40,000 Californians struggle with this incurable disease. Any improvement to their conditions will be of tremendous value for them, and their loved ones.
Funds Requested	$1,399,800
GWG Recommendation	***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 average of the individual member scores. Additional parameters related to the score are shown below.

Mean	83
Median	85
Standard Deviation	9
Highest	95
Lowest	65
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	9
(1-84): Not recommended for funding	5

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	8	3	3

Is the rationale sound?	6	6	2
Is the proposal well planned and designed?	6	3	5
Is the proposal feasible?	7	4	3

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- Huntington's disease is a terrible disease; new strategies are desperately needed.
- The revised application has addressed most of the previous raised concerns.
- There is currently no treatment for HD. Any treatment would be a huge advance in the field.
- Identification of “natural” molecules that could even slow HD would be life-altering for thousands of people.
- The applicants propose to test “natural compounds” of which the virtues have been largely ignored in more recent medicine/research.
- HD patient-derived hiPSCs showed similar phenotype as cells generated containing various repeats.
- There is some worry that screening for compounds in an artificial system could lead to false-positives. This is offset by the ability of the system to screen large numbers of molecules.
- The team is outstanding.

Concerns

- This is an outstanding proposal with some core issues. 1. Can an artificial *in vitro* screen (using human cells – a plus) identify compounds that can help HD patients? 2. Is *in vivo* validation of compounds in an HD mouse model sufficient to move onto the next stage?
- At the request of previous reviewers, the authors have added an *in vivo* study to investigate drug toxicity. Unfortunately, the proposal, as presented, is still lacking justification/rationale.
- The added *in vivo* protocol in zQ175 mice is described only very superficially. A detailed procedure is needed especially relating to time/window of drug delivery. Additionally, using one model of a knock-in HD mouse is not enough. Importantly, there appears to be a lack of knowledge of this mouse model as the timeline proposed to treat these mice does not correspond to the development of the HD-related behavioral and pathological phenotypes associated with these mice.
- Looking at development rather than adult tissue may miss the problem in an adult disease.
- The phenotype of the multinucleated cells is of concern and it’s unclear whether these cells have ever been reported in an *in vivo* context and how relevant are they to the actual human condition.
- The primary assay for drug evaluation is the impact on cells of the ectoderm, mesoderm and endoderm in their germ layer micropattern. This seems too rudimentary and somewhat ambiguous. It is difficult to assess the impact of the drug and this single measure is not enough to conclude efficacy of a drug.
- The major culprit of HD, mHtt, is largely ignored in this grant. Effects of the drug screen do not seem to take this into account.
- It is surprising that the applicants have not begun testing the identified drugs in *in vivo* models. It is also unclear whether these drugs cross the BBB. This is briefly discussed in the pitfall section with a suggestion to use alternative routes of delivery if this is the case.

Application #	DISC2-10188
Title (as written by the applicant)	Immunization strategies to prevent Zika viral congenital eye and brain disease
Research Objective (as written by the applicant)	Our objective is to utilize human iPSC-derived neural and ocular cells to identify growth attenuated and non-pathogenic Zika virus vaccine candidates that can prevent congenital ZIKV disease.
Impact (as written by the applicant)	Currently, there are no therapies or vaccines available against ZIKV for human use. The human iPSC technology provides a unique opportunity to test the growth and virulence of vaccine candidates.
Major Proposed Activities (as written by the applicant)	• Generating recombinant Zika viral vaccine candidates by genetic engineering. • Assessing the growth and virulence of vaccine candidates in iPSC-derived neural and ocular cells. • Characterizing vaccine virus growth and immunogenicity after various routes of administration in adult mice. • Evaluating the safety of vaccine candidates in newborn mice. • Immunization of female mice to limit ZIKV induced congenital disease during pregnancy. • Assessing the vision and neuro-behavior of mice born to immunized mothers.
Statement of Benefit to California (as written by the applicant)	In the past year, millions of people have been infected with Zika virus globally. Currently, the California Department of Public Health has reported 490 travel-associated ZIKV infections including 6 cases of sexual transmission and 82 infected pregnant women (4 live births with microcephaly and eye disease). Mosquitos carrying ZIKV have been reported in California, which increases the risk of local transmission. A ZIKV vaccine can greatly benefit the people in California and beyond.
Funds Requested	$2,206,291
GWG Recommendation	***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 average of the individual member scores. Additional parameters related to the score are shown below.

Mean	82
Median	85
Standard Deviation	4
Highest	85
Lowest	75
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	8
(1-84): Not recommended for funding	6

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	10	1	3
Is the rationale sound?	6	4	4
Is the proposal well planned and designed?	2	7	5
Is the proposal feasible?	8	3	3

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The proposal addresses an unmet medical need.
- There is precedence for using chimeric and directed mutagenesis technology in developing flavivirus vaccines - strong virology background.
- There is an immediate, pressing need to explore options for Zika immunization.
- This work proposes to use hiPSCs in a novel and original way. The route by which vaccines are developed/tested rarely uses hiPSCs and therefore find this to be rather elegant and innovative, opening doors to using such models for unthought-of applications/diseases.
- This idea could very likely accelerate vaccine development, which is normally time consuming. In the context of increased exposure to unknown and new pathogens, this may serve as a solid model in which to develop treatments.

Concerns

- The development plan is incomplete (no TPP for example).
- There are some flawed assumptions. The team lacks a vaccinologist and someone with flavivirus experience outside of hep C which is a flavivirus but much different than dengue, YF< JE, WNV, or Zika.
- Chimeric analysis is reasonable but differences between viral strains not well characterized.
- Experimental rigor and focus must be maintained for this proposal to make progress.
- Retinal infection may be an inflammatory disease, not neural/retinal.
- Limited data is presented with the iPSC modeling of retinal tissue. Also, the ocular phenotype might not be best represented in an iPSC retinal culture.
- There is a concern related to the potential mutation of the Zika virus and the implications this would have on the viability of the vaccine being developed. It is unclear if the vaccine can be easily/quickly modified to account for potential mutations.
- The grant proposal is based on the Asian and African strains. Are there other known strains? Is it just a matter of time before additional strains manifest? Can a co-infection of Dengue and Chikununya (for example), render the vaccine inefficient?

Application #	DISC2-10189
Title (as written by the applicant)	Developing scaling-up differentiation of functioning hepatocytes from hESC using iCELLis bioreactor system
Research Objective (as written by the applicant)	Develop scaling-up differentiation of hepatocytes from hESC using iCELLis nano bioreactors for next translational research using iCELLis 500
Impact (as written by the applicant)	Alternative treatments for liver failure with the use of bioartificial liver device and hepatocyte transplantation will be impacted by available unlimited supply of hepatocytes from these studies.
Major Proposed Activities (as written by the applicant)	• Culture and expand clinical-grade human embryonic stem cells (ESI017) under our xeno-free and feeder-free conditions using a hollow fiber bioreactor and the iCELLis bioreactors • Induce definitive endoderm from human embryonic stem cells and differentiate them towards hepatocytes in the iCELLis bioreactors • Determine the liver function of scaled-up hepatocytes including the values of albumin and urea nitrogen, carbohydrate and lipid metabolism, as well as detoxification and pharmacologic analysis • Develop the cryopreservation of scaled-up for storage and delivery, and determine the viability and liver function after recovery of cryopreserved hepatocytes
Statement of Benefit to California (as written by the applicant)	In California, there are not enough livers available for transplant for people with liver failure. An alternative strategy to improve this situation is the use of bioartificial liver (BAL) device and hepatocyte transplantation. If successful, these liver cells with unlimited supply will be used in clinics for liver failure and severe liver diseases. This project will not only improve health in California, but also bring billions of dollars for California yearly by wide use of these liver cells.
Funds Requested	$2,155,040
GWG Recommendation	***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 average of the individual member scores. Additional parameters related to the score are shown below.

Mean	60
Median	60
Standard Deviation	9
Highest	75
Lowest	40
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	9	4	1

Is the rationale sound?	6	6	2
Is the proposal well planned and designed?	0	11	3
Is the proposal feasible?	0	9	5

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The rationale of the application is important as large-scale production of hepatocyte-like cells will be necessary for future clinical applications. The same for the production of frozen cells.

Concerns

- The lack of preliminary data showing that hPSCs can differentiate into hepatocytes on the bioreactor is a major concern.
- The presentation of the grant proposal needs to be improved. Some parts are unclear and repetitive. Part 3 seems to be missing.
- There is a lack of proof-of-principle for the functionality of generated hepatocytes. There is no point expanding these cells in a large-scale manner or testing cryopreservation before this has been achieved.
- The lack of *in vivo* validations is a major problem. The applicants should plan to validate the hepatocytes generated *in vivo* using an animal model. The preliminary data on FRG mice are interesting but need to be extended.
- The project is too ambitious. Cryopreservation is a grant onto itself.
- The large budget for expanding hESC only is not well-justified.
- The functional characterization of cells is not sufficient to progress to large scale expansion.
- There is insufficient time proposed for the studies to be completed.

Application #	DISC2-10191
Title (as written by the applicant)	Engineered mesenchymal stem cells for combinatorial cancer immunotherapies
Research Objective (as written by the applicant)	We are developing genetically modified stem cells to treat ovarian cancer.
Impact (as written by the applicant)	This work focuses on ovarian cancer, and if successful, the technology can be applied to other solid tumors (e.g. pancreatic, glioma, lung) in the future.
Major Proposed Activities (as written by the applicant)	• Genetic engineering of stem cells to express various therapeutic molecules • Cell culture (in vitro) screening of anti-cancer effect of candidates • Characterize function of anti-tumor stem cells in pre-clinical models of ovarian cancer
Statement of Benefit to California (as written by the applicant)	There is a tremendous unmet need for new and effective therapies for ovarian cancer. In the State of California, it is estimated that there are over 2,000 new cases of ovarian cancer per year with over 1,300 deaths and an annual economic burden of $60M (based on 2013 CDC data). Successful development of a stem cell based therapy for cancer will also support job growth in R&D, manufacturing, and biopharma supporting the novel treatment modality.
Funds Requested	$1,803,602
GWG Recommendation	***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 average of the individual member scores. Additional parameters related to the score are shown below.

Mean	76
Median	75
Standard Deviation	4
Highest	85
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	1
(1-84): Not recommended for funding	14

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	9	0	6
Is the rationale sound?	4	7	4
Is the proposal well planned and designed?	2	6	7
Is the proposal feasible?	2	5	8

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The grant proposal is well-written.
- Reviewers appreciated the combinatorial approach to possibly discover novel synergistic/interactive effects.
- The choice of immune effectors is interesting and the techniques to accomplish MSC payloads are well-described.
- The choice of intraperitoneal administration in mice could be extrapolated to an intraperitoneal approach in humans which may enhance MSC persistence.

Concerns

- The adverse effects of MSCs was not addressed.
- It is uncertain if MSCs last long enough to be of therapeutic value.
- Clinical data regarding MSCs would be helpful.
- A tumor immunologist should be added to the team.
- The reason for the homing of MSCs to tumors needs to be explained. Because MSCs will be targeted by the immune system themselves, it is unclear how will they be maintained.
- The rationale for the different combinations was not clear. A tumor immunologist's expertise would be useful.
- The release kinetics of payloads are missing. If the payloads fail, it may be due to kinetic issues which could be addressed by modifying release/production; studies of release kinetics *in vitro* and correlation to *in vivo* release kinetics may be helpful here.

Application #	DISC2-10193
Title (as written by the applicant)	Stem cell derived exosomes to ameliorate cancer therapy-induced normal tissue injury in the brain
Research Objective (as written by the applicant)	These preclinical studies will discover the best stem cell derived exosome (nanoscale vesicle) based candidate to treat adverse effects of cancer therapy on brain function and cognition.
Impact (as written by the applicant)	Our novel strategy, stem cell-derived exosomes, will address the confounders of stem cells (tumors, immunorejection) and mitigate the debilitating effects of cancer therapy on brain function.
Major Proposed Activities (as written by the applicant)	• Milestone 1: Establish the baseline effect of brain cancer therapy (chemo- and radiation therapy) on cognition using a series of behavioral tests specific to memory and learning centers of the brain. • Milestone 2: Demonstrate the effectiveness of stem cell-derived exosome transplantation to improve cognition in animals receiving chemo- and radiation therapy. • Milestone 3: Determine the ability of exosome transplantation to protect against the adverse effects of cancer therapy on neuronal structure — a determinant of learning and memory. • Milestone 4: Determine the ability of exosome transplantation to improve neuronal function and reduce inflammation — typically impacted by cancer therapy and that contribute to memory impairments. • Milestone 5: Determine early indicators of safety for stem cell-derived exosome transplantation by evaluating tumor formation near to the transplantation site. • Milestone 6: Determine the molecular contents of exosomes that promote functional recovery of the brain and improve cognition after cancer therapy.
Statement of Benefit to California (as written by the applicant)	In California, nearly 105,000 patients diagnosed with cancer will be alive in 5 years and more than 1.4 million have a history of cancer. Importantly, cancer survivors suffer from severe & persistent cognitive impairments that adversely impact quality of life (learning, memory, attention, multi-tasking, planning). Few if any effective treatments exist for this unmet medical need. Our study develops a promising stem cell based therapy to treat the adverse effects of cancer treatment on the brain.
Funds Requested	$1,398,794
GWG Recommendation	***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 average of the individual member scores. Additional parameters related to the score are shown below.

Mean	64
Median	65
Standard Deviation	4
Highest	65
Lowest	50
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

Score Influences
Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	3	7	5
Is the rationale sound?	0	11	4
Is the proposal well planned and designed?	0	13	2
Is the proposal feasible?	0	14	1

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- *None indicated*

Concerns

- The utility of exosomes in recovery to brain injury is an exploratory field. It is not likely that exosome treatment will be ready to advance to a translational phase in two years.
- The proposal does not explain why stem cells are required for exosome preparations, rather than any other neuronal cell type.
- There is a paucity of preliminary data showing the efficacy of exosomes. The best *in vivo* data in Figures 4 and 5 show stem cells (not exosomes) protected against cranial IRR-induced effects. This might support the rationale that stem cells are needed to produce exosomes, except we don't know if exosomes are relevant to the results in Figs 4-5.
- The application does not articulate how the project will progress from discovery to translation.
- If exosomes are effective, the analysis of the biologically active cargo is cursory.
- The lack of attention to previous concerns about exosome characterization and standardization is a great concern. Similarly, the use of three microRNAs as targets for detailed study is without rationale and is not sufficient for standardization purposes.
- The necessary question, of whether this approach would be useful in the clinically relevant context of irradiation combined with chemotherapy, has not been addressed even though such experiments would be straightforward.
- There is no discussion of the problem that only some patients have the cognitive outcomes under concern. Thus, the question for such an experimental therapy is whether clinically developed outcomes can be reversed. This is not addressed, and right now exosome delivery is proposed two days after irradiation.
- There is limited analysis of CNS damage with no attention to white matter changes (which are a serious problem).
- Aim 3 references how the new preliminary data identified three miRNAs but these data are not shown. In addition, the first part of Aim 3 will identify miRNA to be further characterized, which is confusing since the team states that they have already found miRNAs.
- Aim 3 will also focus on “protein cargo.” Very general experiments where any targets will be analyzed *in vitro* and *in vivo* are described with one-sentence descriptions.
- Aim 3 is weak and very underdeveloped.
- Aim 3 focuses on miRNAs. Similar to the original proposal, it is unclear why the team focuses on miRNAs. Many other proteins/molecules likely are present in the exosomes.

Application #	DISC2-10195
Title (as written by the applicant)	Identification and characterization of the optimal human neural stem cell line (hNSC) for the treatment of traumatic brain injury (TBI) 2.0.
Research Objective (as written by the applicant)	We propose to discover the optimal human neural stem cell candidate for traumatic brain injury. 4 hNSC products (2 ES derived & 2 fetal) will be compared with TBI/vehicle controls, & then each other.
Impact (as written by the applicant)	Traumatic brain injury (TBI) affects more Americans than brain, breast, colon, lung and prostate cancer combined! There are no approved stem cell therapies for TBI, we hope to change that.
Major Proposed Activities (as written by the applicant)	• Obtain 2 GMP grade human ES cell lines. Obtain 2 GMP grade human ES cell lines. • Expand/sort ESCs to hNSC and produce sufficient quantities to transplant into 18-20 ATN rats at a dose of 500K per animal. • Test each ES derived hNSC line in an CCI animal model of TBI for efficacy on four different tasks, two for memory and two for emotional changes. • Obtain 2 GMP grade human fetal cell lines. • Expand fetal lines to hNSC and produce sufficient quantities to transplant into 18-20 ATN rats at a dose of 500K per animal. • Test each human fetal derived hNSC line in an CCI animal model of TBI for efficacy on four different tasks, two for memory and two for emotional changes.
Statement of Benefit to California (as written by the applicant)	1.7 million American's experience a Traumatic Brain Injury (TBI) leading to hospitalization (200,000 Californians), at a cost to society of $76.5 billion each year (~$9.3 billion to California). TBI can result in permanent cognitive and emotional deficits. Transplantation of human neural stem cells (hNSCs) could lead to improvements in learning & memory, or emotion that could significantly change a patient's quality of life and have considerable economic impact to the people of California.
Funds Requested	$1,671,213
GWG Recommendation	***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 average of the individual member scores. Additional parameters related to the score are shown below.

Mean	86
Median	85
Standard Deviation	9
Highest	100
Lowest	75
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	8
(1-84): Not recommended for funding	7

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	12	2	1
Is the rationale sound?	7	5	3
Is the proposal well planned and designed?	9	2	4
Is the proposal feasible?	10	2	3

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- An excellent proposal that is highly responsive to previous critiques.
- There is a tremendous need to develop better approaches.
- An excellent team to work on neuroepithelial transplants.
- This is a very strong team working on an important problem. There is high confidence that at the end of the study the team will have evidence on whether or not NSCs are a potential candidate for pre-clinical studies on a focal injury model of TBI.
- The behavioral data, although limited, seems to be comparable to other publications in the field, suggesting that this is a viable approach.
- The importance of this problem merits, to this reviewer, a willingness to take a risk on this team and project.

Concerns

- TBI manifests in an extremely heterogeneous way within the population. This is disregarded in the grant. The applicant does not discuss how cell replacement therapy would be applied in humans. Each individual affected by TBI would present with a unique lesion: site, extent, severity, duration of symptoms.
- There are concerns about local treatment strategy for a diffuse disease process.
- Non-compelling preliminary data.
- Importantly, the animal model suggested to test the efficacy of this method is flawed in the sense that it does not reproduce the main features of TBI in humans. The fact that the trauma may affect small vs. large regions, various regions of the brains, is not taken into account in a model that systemically lesions one area of the hippocampus.
- The diffuse nature of TBI does merit studies on a model that more closely resembles the most frequent human clinical situation.
- It is unclear how one could possibly standardize stem cell therapy to account for this. The applicant does not know or have control over the cell types the stem cells differentiate into after transplantation. This is critical if you are going to inject cells in very distinct parts of the brain all characterized with unique sets of cells.
- The behavioral measures are equally inappropriate in the sense that this may not be at all what we are trying to treat in patients.

Application #	DISC2-10199
Title (as written by the applicant)	Development of a new therapeutic for directing target specific stem cell migration and treatment
Research Objective (as written by the applicant)	A drug-stem cell combination therapy wherein the drug will direct and promote the delivery and distribution of stem cells to the disease site for the optimal therapeutic effect of the stem cells
Impact (as written by the applicant)	Amyotrophic lateral sclerosis (ALS) and the way to deliver and enhance stem cell-based treatment of ALS
Major Proposed Activities (as written by the applicant)	• Complete the additional in vitro studies and initiate the in vivo studies in SOD1 mouse model • Determine whether the combined effect of hNSCs intraspinally augmented & guided by SDV1a has a synergistic effect on improving disease onset/progression & symptom-free survival in the SOD1 mouse • Establish the preliminary toxicity and pharmacokinetics profiles of SDV1a in mouse model • Elucidation of structure and other characteristics; Development and validation of analytical procedures • Process development and characterization in lab scale, stability study
Statement of Benefit to California (as written by the applicant)	This new therapeutic will address a significant unmet medical need in the treatment of amyotrophic lateral sclerosis and have an important impact on the healthcare and bio industry in California.
Funds Requested	$1,906,900
GWG Recommendation	***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 average of the individual member scores. Additional parameters related to the score are shown below.

Mean	67
Median	70
Standard Deviation	8
Highest	80
Lowest	55
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	7	7	0
Is the rationale sound?	3	7	4
Is the proposal well planned and designed?	1	10	3

Is the proposal feasible?	0	11	3

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- Reviewers appreciate the innovation of taking a wild-type biological macromolecule that has both beneficial and harmful actions, and re-engineering it to retain just the beneficial actions.
- There is merit in further developing/improving this type of treatment option. The applicants are also proposing to promote cell migration via a compound they have designed and produced to have such capacities, adding value to their approach by enhancing the effects of stem cells transplanted in fewer sites.
- The preliminary work showing significant increased longevity in treated mice is encouraging and impressive.
- Overall theory is bold and interesting.
- The project builds on solid expertise and similar previous funding from CIRM to this group for such work.

Concerns

- Data pertaining to histological evaluation of migration (Figures 4,7,10, 12) are subpar and not convincing. Another concern is that some of this preliminary data seem to be derived from a single mouse (based on statement in Figure 6).
- The stem cells are injected in one hemisphere while the guidance molecules are injected on the contralateral side. Cells that have migrated are identified two weeks later in the contralateral hippocampus and cortex raising two important issues: 1) their guidance molecule is diffusing from the infusion site which could give rise to non-specific targeting; 2) the molecule is not as specific as the applicants claim and act via mechanisms other than CXCR4.
- It is not indicated whether endogenous stem cells express the CXCR4 receptors. If so, it is unclear how the migration of endogenous stem cells will be prevented after injection of the SDV1 molecule.
- Project is feasible but pitfalls are completely ignored.
- PI received a 24-month CIRM grant ending in 2009 to develop the compound to be tested in the current proposal. No publications have been reported to CIRM that cite this award.
- It is not clear that this proposal will lead to any clinical impact.
- The peptide by itself as a control is missing.
- The written proposal has several grammatical and 'cut and paste' errors.

Application #	DISC2-10203
Title (as written by the applicant)	Dynamic scaffolding system to enhance lineage-specific differentiation and downstream functionality of induced pluripotent stem cells
Research Objective (as written by the applicant)	This study will develop a stem cell culture system which will improve the differentiation efficiency and downstream functionality of stem cells for enhanced therapeutic applicability.
Impact (as written by the applicant)	It will improve current inefficient stem cell differentiation methods to produce clinically applicable cells in a cost-effective manner.
Major Proposed Activities (as written by the applicant)	• Optimize multi-functional scaffolds for enhanced material properties and biocompatibility • Develop a high-throughput cell culture system with on-demand mechanically tunable scaffolds • Determine the effects of stage-dependent temporal control of the mechanical microenvironment on stem cell differentiation
Statement of Benefit to California (as written by the applicant)	This project seeks to advance the safety and effectiveness of the use of stem cells for regeneration of damaged tissues in patients by developing a novel technology. The project speaks directly to the mission of CIRM, particularly to improve human health of California's rapidly growing population by improving stem cell-based therapies. The commercialization of the full-scale system would benefit the people in California with the financial impact of increased employment and tax revenues.
Funds Requested	$804,254
GWG Recommendation	***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 average of the individual member scores. Additional parameters related to the score are shown below.

Mean	75
Median	75
Standard Deviation	3
Highest	85
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	1
(1-84): Not recommended for funding	14

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	7	2	6
Is the rationale sound?	6	4	5
Is the proposal well planned and designed?	1	11	3
Is the proposal feasible?	2	7	6

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The technology is potentially very powerful. For example, would it be useful for protecting pancreatic endocrine progenitor cells or terminally differentiated cells in 96-well or 384-well small molecule screens for incretins or differentiation factors?
- It is an important technology which could improve generation of beta like cells.

Concerns

- The application does not focus on the right aspect. It should focus on the production of fully functional differentiated cells.
- It is unclear how this technology will be transferred to the clinic.
- The biology could be stronger.
- It is unclear that mechanics alone are sufficient for this particular differentiation.
- The dynamic scaffolding system is well described but the biological utility, compared with current technology, is not compelling.
- The timeline focuses on issues of scaffold properties and high throughput device fabrication but not transition to production of a stem cell product for clinical studies.
- Pitfalls and alternatives focus on technical issues, not improved production of hormone producing cells.
- There is insufficient detail provided in the preliminary data.

Application #	DISC2-10205
Title (as written by the applicant)	A synergistic stem cell therapy for juvenile macular dystrophy
Research Objective (as written by the applicant)	Combined treatment for juvenile macular dystrophy-subretinal injection of iNPCs to preserve local vision (Macular in human) and systemic infusion of MSCs to improve retinal homeostasis
Impact (as written by the applicant)	If efficacy and safety are established, these combined stem cell therapy can be quickly translated into clinical trial to treat juvenile macular dystrophy
Major Proposed Activities (as written by the applicant)	• Cell production and characterization: iNPCs, MSCs derived from wild type mouse and blood derived iPSCs (iMSC). • To determine whether combined stem cell treatments in autosomal dominant, fast degeneration model for Stargardt disease (STGD)-Elovl4 mice at early and mid-stage of degeneration will rescue vision. • To determine whether combined stem cell treatments in autosomal recessive, slow degeneration model for STGD-ABCA-4- at early and mid-stage of degeneration will slow down the disease progression. • To investigate whether iMSCs derived from human iPSCs as supplementation to subretinal injection of iNPCs will have a synergistic effect in rescuing vision in fast degeneration Elovl4 mice for STGD. • To investigate mechanism of the combined stem cell treatments in rescuing vision
Statement of Benefit to California (as written by the applicant)	Stargardt disease (STGD) is the most common form of inherited juvenile macular degeneration has tremendous financial and social consequences. Children diagnosed with STGD are most in need of vision–preserving therapies. The combined treatments overcome hurtle and advances the field. if safety and efficacy are established, this approach can be quickly translated into clinical trail for juvenile macular dystrophy. Slowing down disease progression will have huge impact to patients and society.
Funds Requested	$1,828,023
GWG Recommendation	***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 average of the individual member scores. Additional parameters related to the score are shown below.

Mean	67
Median	70
Standard Deviation	4
Highest	70
Lowest	60
Count	12
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	12

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	8	3	1
Is the rationale sound?	1	10	1
Is the proposal well planned and designed?	0	9	3
Is the proposal feasible?	0	8	4

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- *None indicated*

Concerns

- The rationale is based on an assumption that NPCs as an alternative cell type to RPE does not require attachment to BM while offering vision preservation and reducing the burden of diseased RPE.
- The mechanism of action behind this therapeutic effect is unclear.
- Better outcomes when transplanting iNPCs vs. RPE is the main hypothesis, but no direct comparisons are planned.
- Combining iNPCs and MSCs is very complex and might be difficult to transfer to the clinics. MSCs are not needed.
- There is no clear plan to transfer this approach to the clinic.
- The intent of using several animal models with different pathophysiology is not clearly explained and the mechanism by which iNPSCs will help are unclear.
- There is an assumption that iNPCs work by improving phagocytosis but this is not a significant defect in the Stargardt mouse models (photoreceptor rather than RPE disease).
- It is unclear that systemic MSCs will add significantly to the therapeutic effect - also systemic toxicity of MSCs has not been included in the study.
- It is unclear if iNPCs injected subretinally will work long term.

Application #	DISC2-10213
Title (as written by the applicant)	Engineering Live Meniscus Tissue by Electrospinning and Electrospraying Stem Cells
Research Objective (as written by the applicant)	A nano-engineered tissue construct possessing properties comparable to the native meniscus that can reconstruct lost meniscal tissue and can prevent secondary knee osteoarthritis.
Impact (as written by the applicant)	Meniscal injury and surgery is the most common orthopaedic condition affecting over 600,000 every year. We propose to prevent secondary arthritis after meniscal damage.
Major Proposed Activities (as written by the applicant)	• Differentiate pluripotent cells into meniscal progenitors • Engineer a biomimetic scaffold properties of human meniscus • Repair ex vivo meniscal defects using live tissue-engineered constructs • Demonstrate efficacy of meniscal reconstruction in vivo
Statement of Benefit to California (as written by the applicant)	A stem cell-based approach for treating meniscal lesions is not represented in CIRM's current Translation Portfolio. This application addresses an unmet medical need that, if successfully developed and made available to patients, will represent a significant improvement upon the current standard of care.
Funds Requested	$1,886,146
GWG Recommendation	***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 average of the individual member scores. Additional parameters related to the score are shown below.

Mean	66
Median	65
Standard Deviation	3
Highest	75
Lowest	65
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	9	4	1
Is the rationale sound?	2	10	2
Is the proposal well planned and designed?	0	10	4
Is the proposal feasible?	0	9	5

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- A solid, integrated project to address the entire "ecosystem" or "biological environment" for regenerating cartilage---electro-spinning/ -spraying/ cellular constituents/ growth factors.
- The project is logically organized with a very aggressive timeline which should be implementable.

Concerns

- The potential immunogenic responses to the MSCs, despite the short-term sheep data, are concerning. Furthermore, in preparation for the pre-IND meeting, there will need to be much more specificity about the methodology within the protocol (i.e., dose of growth factors, duration of electrospraying, etc).
- The applicants claim “no evidence of cell migration out of electrospun scaffold in *in vivo* experiments”, but data is not shown (in addition, Fig 3 claims to show a 4-week time point but the image is of 3-week tissue).
- Figures 4-7 (there are two figure 6s), appear to support the use of cells to heal damaged tissue. These data are poorly described and the figures are not referenced in the text.
- It is not clear where the large animal work (sheep) will be performed.
- It is not clear who on the team has expertise in creating meniscal tears and working with the model system.
- The imaging center specifically says that it can do small animal imaging. No mention of large animal imaging. Unclear how sheep samples will be processed.
- The choice of cells is a major issue.
- There is a lack of experimental details.
- The proposal lacks novelty. Electrospinning and electrospraying has been used before.
- The proposal is poorly written. There are several grammatical errors in the proposal.