TOTAL BUDGET: DISC 1 2016

TIER 1 $4,020,878

TIER 2 $8,336,719

App #	Title	Score	Median	SD	Low	High	Budget	Tier	T1	T2
DISC1-08825	Reverse transcriptase inhibitors as a novel therapeutic approach for	98	99	2	95	100	$232,200	1	15	0
DISC1-08723	iPS-Interneuron Transplantation for Neural Repair after Stroke	95	95	2	90	97	$229,396	1	15	0
DISC1-08792	Generation of bile duct-competent transplantable human liver orga	91	90	2	89	95	$206,460	1	15	0
DISC1-08731	Autologous iPSC-based therapy for radiation induced bladder injur	91	90	2	85	95	$237,564	1	15	0
DISC1-08848	Embryonic Stem Cells for Corneal Endothelial Degeneration	90	90	1	90	92	$237,564	1	14	0
DISC1-08800	Blood Brain Barrier (BBB)-on-Chip: Development and validation of a	90	90	3	85	94	$241,992	1	14	0
DISC1-08855	Modulating Liver Sinusoidal Endothelial Cell Permeability to Enhanc	90	90	0	90	90	$180,000	1	14	0
DISC1-08652	Examining the efficacy of GDF11 antibody as a rejuvenator of aged	90	90	3	85	95	$180,000	1	15	0
DISC1-08819	Organoid Modeling of Human Cortical Microcircuits	90	90	6	70	97	$230,400	1	14	1
DISC1-08790	Targeting progenitors in scar tissue to reduce chronic scar burden	90	90	2	85	92	$230,400	1	14	0
DISC1-08842	Identification of stem cell surface markers as potential therapeutic ta	90	90	1	85	92	$230,400	1	14	0
DISC1-08650	Activation of patient-specific endogenous myocardial repair througl	90	90	1	85	90	$236,338	1	15	0
DISC1-08823	Novel Platforms to Enhance In Vivo Delivery of Skeletal Muscle Prog	88	87	3	85	95	$230,400	1	15	0
DISC1-08868	Developing a personalized approach to beta cell replacement for pa	86	86	4	80	95	$180,000	1	11	3
DISC1-08737	New Methods for the Chemical Expansion of Hematopoietic Stem a	86	85	2	85	90	$232,200	1	15	0
DISC1-08683	Microenvironment based optimization of retinal induction using CRI	86	85	2	80	90	$232,200	1	13	1
DISC1-08750	Curing bladder cancer by replacing corrupted urothelium with diffe	85	86	6	75	100	$237,564	1	11	3
DISC1-08776	Genome editing for causation and reversion of MPN-associated mut	85	85	3	80	90	$235,800	1	11	4
DISC1-08933	Splicing Modulators as Leukemia Stem Cell Inhibitors in Acute Myel	84	85	4	75	90	$150,000	2	11	3
DISC1-08910	Reprogramming human stem cells for blood cell generation	84	85	4	75	90	$232,200	2	11	4
DISC1-08643	Exosomal Y-RNAs as mediators of bioactivity of cardiac-derived cell	84	85	2	80	88	$181,063	2	10	4
DISC1-08813	IVD regeneration using iPSC-derived NP-progenitors in organ cultur	84	85	3	75	88	$236,484	2	12	3
DISC1-08878	Functional characterization of pluripotency exit-associated enhancer	83	85	9	65	99	$209,000	2	9	5
DISC1-08789	Targeting cancer stem cells in an orthotopic patient-derived xenogr	83	85	5	72	90	$176,535	2	8	7
DISC1-08711	Bone-healing cartilage derived from human pluripotent cells for the	82	80	6	75	95	$250,200	2	7	8
DISC1-08651	Investigation of pathogenesis in human Huntington's Disease striata	82	82	4	75	90	$241,992	2	6	9
DISC1-08777	Stem Cell Maintenance in Falconi Anemias by Pharmacologic Modu	81	80	2	80	85	$237,564	2	3	12
DISC1-08828	Genomic analyses of single human hepatocyte stem cells	81	80	8	60	95	$237,564	2	5	10
DISC1-08891	Novel chondroprotective agonists of gp130 signaling	81	80	3	75	85	$250,200	2	4	11

TOTAL BUDGET: DISC 1 2016

TIER 1 $4,020,878

TIER 2 $8,336,719

App #	Title	Score	Median	SD	Low	High	Budget	Tier	T1	T2
DISC1-08720	Development of Liver Organoids from iPSCs to Treat Hemophilia A	78	80	6	70	88	$235,800	2	4	11
DISC1-08698	Targeting IGF1 signaling pathway to promote hematopoietic stem c	76	75	2	75	80	$234,270	2	0	15
DISC1-08914	Human induced pluripotent stem cell-derived cardiomyocyte engra	76	75	3	70	80	$221,441	2	0	13
DISC1-08834	Developing new methods to monitor ES and iPS cell-derived humar	75	75	9	60	85	$230,400	2	3	12
DISC1-08733	Interleukin-10 producing Mesenchymal Stem Cells for the treatment	74	75	5	70	85	$235,588	2	1	14
DISC1-08856	Cardiac disease modeling in pig hearts using human ARVD patient-	72	70	4	65	80	$229,310	2	0	15
DISC1-08882	Matching Cell Grafts to Patients: A Tissue-Engineering Approach to	71	75	12	50	84	$235,800	2	0	15
DISC1-08596	Development of a hematopoietic stem cell growth factor	69	70	10	35	75	$232,200	2	0	15
DISC1-08692	Generation of vascularized cerebral motor cortex organoids for trea	69	70	6	50	75	$235,800	2	0	15
DISC1-08637	Dynamic control of scaffold stiffness for efficient stem cell differentia	68	70	7	55	82	$172,996	2	0	14
DISC1-08796	In vivo screen for small molecules that regulate human hematopoiet	66	70	10	45	84	$222,480	2	0	14
DISC1-08727	Adipose-derived native perivascular mesenchymal stem cells for tre	65	65	3	60	70	$250,200	2	0	15
DISC1-08601	Anti-inflammatory mesenchymal stem cells 2 (MSC2) for the treatme	65	72	24	1	85	$298,422	2	2	12
DISC1-08798	The impact of regulatory T cells on neural precursor cell induced rer	65	65	0	65	65	$202,680	2	0	14
DISC1-08899	Cell therapy for Type 1 Diabetes using a novel thin-film encapsulatic	64	65	5	55	75	$172,984	2	0	14
DISC1-08913	Transcriptional profiling of human bioengineered kidney organoids	61	60	7	50	75	$222,026	2	0	14
DISC1-08782	Transplantation of GDNF-expressing neural progenitor cells to treat	60	60	1	60	65	$241,992	2	0	14
DISC1-08681	Analyzing Epigenetic Memory In Vivo to Uncover Regulators of Hem	Below 60	---	---	---	---	$237,564	2	2	12
DISC1-08799	A Novel Method for Deriving Neuronal Progenitors for Parkinson's D	Below 60	---	---	---	---	$250,240	2	0	15
DISC1-08886	Single Cell Deconvolution of Mesodermal Priming from the Human	Below 60	---	---	---	---	$237,564	2	0	14
DISC1-08940	Development of a Novel Human Neural Cell Based Drug Screening	Below 60	---	---	---	---	$202,500	2	0	13
DISC1-08766	Identification of novel targets through neurotransmitter regulation c	Below 60	---	---	---	---	$255,420	2	0	15
DISC1-08721	Deciphering the genetic mechanisms of Parkinson's diseases for imp	Below 60	---	---	---	---	$238,500	2	0	14
DISC1-08784	Establishment of human cancer stem cell lines from patients for elim	Below 60	---	---	---	---	$235,800	2	0	14
DISC1-08845	Sending foes against foes – Using genetically modified cancer stem	Below 60	---	---	---	---	$180,000	2	0	14
DISC1-08906	Using patient-specific hiPSCs to generate engraftable immunocomp	Below 60	---	---	---	---	$221,940	2	0	14

Public Summary for DISC1-08596

Application #	DISC1-08596
Title (as written by the applicant)	Development of a hematopoietic stem cell growth factor
Research Objective (as written by the applicant)	The main goal of the proposed studies is to develop a recombinant WNT protein for use as a stem cell factor to promote the development of blood stem cells from human pluripotent stem cells.
Impact (as written by the applicant)	Developing a robust method to derive blood stem cells from patient-specific pluripotent stem cells will revolutionize medicine by providing unlimited numbers of cells suitable for transplantation.
Major Proposed Activities (as written by the applicant)	• A novel blood stem cell growth factor, called WNT9A, will be isolated in purified form and its activity will be quantified in standard assays. • The WNT9A protein will be used to improve on existing differentiation protocols to derive blood stem cells from human pluripotent stem cells.
Statement of Benefit to California (as written by the applicant)	This research will yield two deliverables with significant therapeutic and economic value. First, a novel Wnt protein will be purified and characterized. Other Wnt proteins are currently being produced by several companies and are used for basic research and more recently for cell and tissue engineering. Second, this research will provide an alternative source of therapeutic blood stem cells, which would be a boon to the field of regenerative medicine.
Funds Requested	$232,200
GWG Recommendation	***Tier 2 – Not recommended for funding.***

Final Score: 69

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.

Median	70
Standard Deviation	10
Highest	75
Lowest	35
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (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?	5	5	5
Is the rationale sound?	4	4	7
Is the proposal well planned and designed?	2	5	8
Is the proposal feasible?	4	1	10

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 a strong basis for investigating Wnt9a.
- The expertise in Wnt and hematopoietic stem cell differentiation is strong.

Concerns

- Concerns exist about the relative paucity of functional assays. For example, there is a lack of functional evaluation of hematopoietic stem cells.
- Aim 2 should be better focused on functional testing of Wnt9a effects on hematopoietic stem cells generation.

- Devising functional tests should be a priority in this research plan.

Additional Comments

- The first aim is to produce recombinant protein, which is necessary but not transformative.

Public Summary for DISC1-08601

Application #	DISC1-08601
Title (as written by the applicant)	Anti-inflammatory mesenchymal stem cells 2 (MSC2) for the treatment of Huntington's disease
Research Objective (as written by the applicant)	The overall goal of our study is to demonstrate efficacy of a new anti-inflammatory mesenchymal stem cell-based product, "MSC2" cells, in established mouse models of Huntington's disease.
Impact (as written by the applicant)	The demonstration of efficacy of our MSC2 treatment in HD mouse models will advance a novel anti-inflammatory stem cell-based product for the safe and effective treatment of Huntington's disease (HD).
Major Proposed Activities (as written by the applicant)	• We will determine the safety and efficacy of anti-inflammatory MSC2 treatment over conventional MSC treatment in two different mouse models of Huntington's disease. • We will identify potential mechanisms of action in MSC2 efficacy by measuring inflammatory markers in brain and blood of treated HD mice.
Statement of Benefit to California (as written by the applicant)	Approximately one in 10,000 CA residents has HD, which has no effective treatment or cure and results in enormous financial and emotional costs for friends, families and caregivers. California has a particularly strong HD community, including researchers, physicians, patient advocates and caregivers all working together towards finding a treatment for this devastating disorder. Our work should lead to the development of a new stem cell-based treatment for HD patients.
Funds Requested	$298,422
GWG Recommendation	***Tier 2 – Not recommended for funding.***

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.

Median	72
Standard Deviation	24
Highest	85
Lowest	1
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	2
Tier 2 (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?	5	6	3
Is the rationale sound?	2	9	3
Is the proposal well planned and designed?	1	7	6
Is the proposal feasible?	1	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 research is focused on Huntington's disease (HD) and has good medical relevance. Select MSC lines may have neuroprotective effects. The role of inflammation is also relevant and of interest and may be central to HD.
- This is potentially a very interesting idea that uses a potential immunomodulation to positively influence HD.
- The beneficial effect is specific to the anti-inflammatory MSC2 preparation, which is consistent with the overall hypothesis of a role of inflammation in HD.
- The interaction with a company partner is a strength.

- Translation into a clinical trial is highly feasible and the cell product seems to be highly standardized and thus useful for therapeutic application.

Concerns

- The data indicating a benefit of cell delivery is not very convincing.
- Analyses at the tissue level are quite superficial, and thus it is not clear how much these analyses will reveal HD-relevant benefits.
- Reviewers expressed concerns about low animal numbers and statistical significance.
- Mouse models of HD have very few presentations as seen in human disease, making the lack of benefit even more problematic.

Additional Comments

- The approach is novel and risky and while the preliminary data are limited there seems to be some validity to try this approach.
- The applicant needs more samples to reach statistical power to move forward. This can be achieved through this application.

Public Summary for DISC1-08637

Application #	DISC1-08637
Title (as written by the applicant)	Dynamic control of scaffold stiffness for efficient stem cell differentiation
Research Objective (as written by the applicant)	The objective of this study is to examine the effects of dynamically and precisely controlled physical conditions on stem cell differentiation.
Impact (as written by the applicant)	This study will result in the development of efficient stem cell technologies leading to affordable stem cell-based therapies.
Major Proposed Activities (as written by the applicant)	• Develop a cell culture system that can subject cells to mechanically varying environment. • Test how stem cells behave under mechanically varied conditions during differentiation to target cell types.
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 the patient's body by developing a novel technology. The project speaks directly to the mission of CIRM, particularly to improve human health for California's rapidly growing population by 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	$172,996
GWG Recommendation	***Tier 2 – Not recommended for funding.***

Final Score: 68

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.

Median	70
Standard Deviation	7
Highest	82
Lowest	55
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (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?	5	8	2
Is the rationale sound?	4	6	5
Is the proposal well planned and designed?	0	10	5
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

- Aim 1 would develop a useful tool to study dynamic effects of substrate stiffness on stem cell differentiation.
- The data showing that scaffold “stiffness” can drive differentiation efficiency differences is intriguing.
- The characterization of how mechanical microenvironments affect stem cell differentiation by changing scaffold stiffness would advance the field.

Concerns

- There is no scientific approach in Aim 2 to evaluate magnitude and timing of stiffness on cell differentiation.
- The path forward is not presented. It seems to be assumed that the next step will be scale-up of the current experiment, but no details are provided. It is unclear how would this be scaled to translational applications in subsequent work.
- Using the proposed markers, it may be difficult to conclude that the desired cell types have been achieved.
- No mechanism of action is described.
- Some concerns on non-uniformity of membrane after spinning were expressed and not suitably addressed in the proposal.

Additional Comments

- The study of substratum stiffness on differentiation is partially novel. There is concern that there is no attempt to identify the mechanism.

Public Summary for DISC1-08643

Application #	DISC1-08643
Title (as written by the applicant)	Exosomal Y-RNAs as mediators of bioactivity of cardiac-derived cell therapy.
Research Objective (as written by the applicant)	We propose to dissect the contribution of Y-RNAs, small non-coding RNA species enriched in CDC-exosomes, in mediating the effect of CDC-exosomes on cardioprotection and macrophage polarization.
Impact (as written by the applicant)	Examining the contribution of highly represented RNA species in CDC-exo could allow a better understanding of the mechanism of action of CDC-exo and modulation of their cargo to enhance their potency.

Major Proposed Activities
(as written by the applicant)
	• Epigenetic reprogramming.
	  ○ Effect of Y-RNA on the heritable changes in gene activity and expression that occur without alteration in DNA sequence, which could explain the sustained effects of CDC-exo.
	• Cardioprotective role of Y-RNA is correlated with macrophage polarization.
	  ○ In vitro analyses of the anti-inflammatory pathway mediated by Y-RNA (IL10, anti-inflammatory cytokine, increase by Y-RNA).
	• Structural analyses of Y-RNA fragment.
	  ○ Generation of mutated fragments resulting in a change in the secondary structure that could affect the function.
	• Functional analyses of the Y-RNA/hnRNPH1 complex in crucial aspects of RNA processing (pre-mRNA splicing...) in normal and pathological conditions.

Statement of Benefit to California (as written by the applicant)	About 610,000 men and women die each year from heart disease in the US (1 in every 4 deaths), motivating the development of more effective therapeutic strategies. We propose to characterize the implication of Y-RNA, highly enriched in CDC-exosomes, in mediating cardioprotection following a heart attack. This characterization will allow a safe modulation of exosomal RNA content, opening up the possibility that exosomes may become next-generation off-the-shelf therapeutic products.
Funds Requested	$181,063
GWG Recommendation	***Tier 2 – Not recommended for funding.***

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.

Median	85
Standard Deviation	2
Highest	88
Lowest	80
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	10
Tier 2 (1-84): Not recommended for funding	4

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	3
Is the rationale sound?	9	1	4
Is the proposal well planned and designed?	5	4	5
Is the proposal feasible?	5	3	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 focus on Y-RNA is reasonable based on the presented preliminary data and the need to define a mode of action for cardiopshere-derived cells (CDC)-therapeutics.
- This proposal may lead to novel treatment options; the research may yield insights into the cardioprotective mechanism of CDCs.
- The preliminary data is a major strength.

Concerns

- The Principal Investigator has limited experience in the field, which together with absence of preliminary data causes some concerns.
- There is concern regarding species mismatch; the study should be performed exclusively in human cells (CDC, macrophages and cardiomyocytes).

Additional Comments

- The proposal aims to understand the functional mechanisms related to Y-RNA.

Public Summary for DISC1-08650

Application #	DISC1-08650
Title (as written by the applicant)	Activation of patient-specific endogenous myocardial repair through the exosomes generated from the hypoxic iPSC-derived cardiomyocytes (iCMs).
Research Objective (as written by the applicant)	This proposal will provide direct evidence of clinical implementation of patient-specific iPSC products by validating the efficacy of autologous, cell-free exosome therapy.
Impact (as written by the applicant)	Five-year survival of heart failure is a dismal 50% and is top diagnosis of hospital admission. Exosomes offer a feasible and effective cell-free therapy by activating endogenous myocardial repair.
Major Proposed Activities (as written by the applicant)	• The exosomes from the injury and non-injury models of human iCMs are generated, quantified, isolated, and analyzed for their miRNA content. • Functional benefit of injured and non-inured exosomes and their corresponding miRNAs is assessed following direct injection into the injured murine myocardium, using advanced MRI and molecular assays. • Autologous exosomes and their miRNAs derived from the injured iCMs are re-administered to the iCMs to assess the efficacy of activating endogenous self-repair and elucidate the mechanism of action. • Changes in the molecular, cellular and functional property of the injured iCMs are measured after the re-administration of the exosomes and miRNAs to determine the in vitro restorative effects. • Changes in fibrosis, hypertrophy, remodeling, and apoptosis genes are measured by microarray, cell injury through flow cytometry, and contractile force via atomic force microscopy. • Electrical activity is measured via patch clamp to quantitate the direct electrophysiologic effects of the exosomes on iCMs. The functional assays listed here are well established in our laboratory.
Statement of Benefit to California (as written by the applicant)	Five-year survival of heart failure (HF) is a dismal 50% and a leading diagnosis of hospital admission in California. Autologous exosomes may offer a feasible, effective therapy by activating endogenous repair of the injured heart. This study allows systematic analysis of the feasibility of cell-free therapeutic paradigm generated from patient- and injury-specific iPSC-derivatives. The exosomes will circumvent the challenges of stem cell therapy and provide effective therapy for all patients.
Funds Requested	$236,338
GWG Recommendation	***Tier 1 – Exceptional merit and warrants funding, if funds are available.***

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.

Median	90
Standard Deviation	1
Highest	90
Lowest	85
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	15
Tier 2 (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?	13	0	2
Is the rationale sound?	13	0	2
Is the proposal well planned and designed?	14	0	1
Is the proposal feasible?	13	0	2

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 contains a very strong research plan and team.
- The strongest part is the *in vitro* simulation of an autologous treatment scenario (Aim 2).
- Clinical relevance is high.
- There is compelling preliminary data.
- The experimental design is sound

- Pitfalls are identified and ways to address them are proposed.
- Uniformly positive support for this grant due to potentially high impact.
- The proposal is highly feasible and well designed.

Concerns

- No relevant concerns were expressed by the GWG.

Additional Comments

- Increasing our understanding of the role of exosomes is important.
- Human MSC exosomes seem to have an effect in the mouse. This is a bit surprising as it may not be due to specific effects because of the species mismatch.

Public Summary for DISC1-08651

Application #	DISC1-08651
Title (as written by the applicant)	Investigation of pathogenesis in human Huntington's Disease striatal medium spiny neurons derived from iPSCs.
Research Objective (as written by the applicant)	Our strategy proposes to use patient iPSCs and isogenic controls directly differentiated into the specific striatal neurons lost in Huntington's disease (HD) to assay for specific aspects of disease.
Impact (as written by the applicant)	If this idea were successfully realized it would provide the preliminary evidence (substantiated HD phenotypes in human patient at-risk tissues) to generate a drug-discovery platform for HD.
Major Proposed Activities (as written by the applicant)	• Generation of isogenic gene-corrected control iPSC lines from HD patient iPSCs. • Immunocytochemistry to assay for specific cell generation and protein aggregation. • Electrophysiology to assay for specific neuron generation and known disease phenotypes. • Live cell imaging to assay for cell death over longitudinal study.
Statement of Benefit to California (as written by the applicant)	Huntington's disease (HD) is a fatal autosomal dominant neurodegenerative disorder affecting over 30,000 people in the US, with another 150,000 currently at risk. Our strategy proposes to use patient iPSCs and isogenic controls forced into the specific striatal neurons lost in disease as a potential drug discovery platform and/or novel cell replacement therapy for HD, thus greatly benefiting the residents of the State of California.
Funds Requested	$241,992
GWG Recommendation	***Tier 2 - Not recommended for funding.***

Final Score: 82

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.

Median	82
Standard Deviation	4
Highest	90
Lowest	75
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	6
Tier 2 (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	1	5
Is the rationale sound?	4	4	7
Is the proposal well planned and designed?	3	2	10
Is the proposal feasible?	5	0	10

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 proposed project explores a novel idea – the fast generation of medium spiny neurons (MSNs) from patient-specific induced pluripotent stem cells.
- Advantages of rapid differentiation are very significant.
- Opportunity for assessing the cell differentiation effect of mutant huntington by reverting the isogenic lines thereby controlling for the effects of genetic background and idiosyncrasy.
- Excellent medically significant impact possible. Strong grant with good concept and preliminary data.

Concerns

- A more sophisticated molecular assessment would be valuable so that the degree to which the cells actually match MSNs can be assessed.
- Progression of the proposal is not clear.
- The use of cells for therapeutically relevant discovery processes is very weak.
- It is unclear to what extent the product/technology can be ultimately translated into a therapeutic product or a technology that will improve patient care.
- The progression from a successful pilot study to the next stage(s) is not discussed.
- It is not clear why this approach would be better than CRISPR/Cas9 generation of different repeat lengths directly.
- The presentation of what will be done with the cells in terms of biological outcomes that may reveal interesting principles is weak.

Additional Comments

- No additional comments were expressed by the GWG.

Public Summary for DISC1-08652

Application #	DISC1-08652
Title (as written by the applicant)	Examining the efficacy of GDF11 antibody as a rejuvenator of aged human muscle stem cell capacity and muscle repair.
Research Objective (as written by the applicant)	To examine the efficacy of blocking blood borne GDF11 activity to rejuvenate aged human muscle stem cell regenerative capacity.
Impact (as written by the applicant)	This project will provide a proof-of-principle that GDF11 inhibition can boost aged human skeletal muscle repair, and facilitate its translational potential.
Major Proposed Activities (as written by the applicant)	• Determine GDF11 protein levels in human sera as a function of age. • Determine the efficacy of GDF11 antibody treatment to reverse the effects of aging serum on human muscle stem cell function under transplantation setting. • Determine the efficacy of GDF11 antibody treatment to reverse the effects of aging serum on human muscle stem cell function examined in vitro.
Statement of Benefit to California (as written by the applicant)	The percentage of elderly adults is at a historical high, and continues to climb. The need to develop therapeutic strategies to treat pathophysiological conditions in the elderly is medically and economically relevant. I propose to develop novel approaches for the augmentation of human muscle stem cell function to rejuvenate muscular regeneration and aging. These advances could positively impact the aging population of California, reducing morbidity, mortality, and health care costs.
Funds Requested	$180,000
GWG Recommendation	***Tier 1 – Exceptional merit and warrants funding, if funds are available.***

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.

Median	90
Standard Deviation	3
Highest	95
Lowest	85
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	15
Tier 2 (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?	14	0	1
Is the rationale sound?	13	1	1
Is the proposal well planned and designed?	13	0	2
Is the proposal feasible?	13	0	2

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

- This is a novel idea since the field headed the opposite direction just a couple of years ago.
- The progression to a clinical application is well-spelled out.
- There is controversy in this field. This proposal should, finally, determine the role of GDF11.
- The controversy needs to be resolved. Careful investigation will be extremely valuable.

Concerns

- Increase in GDF11 may serve as a biomarker of aging, but it is unclear how a correlation between age and GDF11 levels will uncover data on stem cell function (as is claimed by the applicant).
- More pitfalls could present themselves, in particular in the animal model, which were not identified.
- All preliminary data shows that overexpression of GDF11 results in muscle defects. The proposed experiments are to decrease GDF11. There is no reason to expect that decreasing GDF11 will have the opposite effect of increasing expression of this gene.

Additional Comments

- No additional comments were expressed by the GWG.

Public Summary for DISC1-08681

Application #	DISC1-08681
Title (as written by the applicant)	Analyzing Epigenetic Memory In Vivo to Uncover Regulators of Hematopoietic Stem Cell Development.
Research Objective (as written by the applicant)	The proposed research is to identify novel regulatory genes that govern developmental HSC emergence and maintenance. The goal of this study is to provide new insights into HSC generation in vivo.
Impact (as written by the applicant)	Hematopoietic stem cell transplantation (HSCT) is the only cure for hematologic diseases. This research will benefit significantly to successful developing and maintaining HSCs.
Major Proposed Activities (as written by the applicant)	• Generate iPSC lines from different somatic cell types (HSCs) and embryonic fibroblasts (MEFs), using a dox-inducible reprogrammable (Oct4, Sox2, Klf4; 3F) mouse. • Generate chimeric offspring in which donor contribution to different lineages can be assayed easily by flow cytometry. • Repeat the above cycle (iPS and chimeras generation); compare the transcriptome, and epigenome of lineage-primed cell lines to uncover deferentially expressed genes related to differentiation bias. • Use a piggyBac system with five inducible (dox) human reprogramming factors (Oct4, Sox2, Klf4, Lin28 and Nanog) to generate reprogrammable human iPSCs. • Various biased HSC-hiPSC lines will be subjected to cyclic programming/reprogramming using teratoma formation system previously established in our lab to generate HSCs and observe the differences. • Transcriptome/epigenetic analysis, and functional validation of the above described lineage-primed cell lines and conclude regulatory genes/pathways for HSC development.
Statement of Benefit to California (as written by the applicant)	Hematopoietic stem cell (HSC) transplantation is the only cure for many severe hematologic diseases. Current scalable protocols for pluripotent stem cell differentiation (PSC) fail to generate HSCs that are functional in vivo. The proposed research is to identify novel regulatory genes that govern developmental HSC emergence and maintenance. Successful completion of this study will thus advance our understanding of the HSC development, and benefit Californian's blood transplantation.
Funds Requested	$237,564
GWG Recommendation	***Tier 2 – Not recommended for funding.***

Final Score: Below 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.

Median	---
Standard Deviation	---
Highest	---
Lowest	---
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	2
Tier 2 (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?	7	4	3
Is the rationale sound?	2	9	3
Is the proposal well planned and designed?	3	6	5
Is the proposal feasible?	2	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

- The proposal is very high risk but may have a potentially high pay off.
- The team is very strong and is likely the only group that may be able to execute such a proposal.

Concerns

- The approach is highly risky, and there are not many details on the experimental design relating to how the cyclical iPSCs will be tested, clonal analysis and other feasibility concerns.

- The rationale is unclear. Aberrant (unstable memory) and not universally agreed upon memory is not a rational way to study HSC development.
- Memory is transient and cells/chimeras are not clonal. Multiple (heterogenous) cells will make the chimera. The HSCs will be heterogenous, and there is no clear description of how this will be addressed with numbers.

Additional Comments

- No relevant comments were expressed by the GWG.

Public Summary for DISC1-08683

Application #	DISC1-08683
Title (as written by the applicant)	Microenvironment based optimization of retinal induction using CRISPR-CAS9 reporter pluripotent stem cells as an expandable source of retinal progenitors and photoreceptors.
Research Objective (as written by the applicant)	To increase the efficiency of generating pure retinal progenitor cultures for use in transplantation and to probe general aspects of retinal development.
Impact (as written by the applicant)	Our methods could increase the efficiency of obtaining transplantable patient specific induced pluripotent stem cell derived retinal cells for the treatment of blindness through cell replacement.
Major Proposed Activities (as written by the applicant)	• Make stem cell based early retinal reporters as tools for optimization. • Optimize cell differentiation, focusing on hypoxia and diffusible factors.
Statement of Benefit to California (as written by the applicant)	California is already a leader in retinal stem cell research with great emphasis placed on transplantation of fetal retinal progenitors. These cells show great promise as a short term tool for cell replacement. The ultimate goal will be to use a patient's own cells for cell replacement and for that to happen PSC technology needs to be further developed. Our work will bolster the work of other California scientists by providing them with new and improved methods for obtaining transplantable cells.
Funds Requested	$232,200
GWG Recommendation	***Tier 1 – Exceptional merit and warrants funding, if funds are available.***

Final Score: 86

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.

Median	85
Standard Deviation	2
Highest	90
Lowest	80
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	13
Tier 2 (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?	9	1	4
Is the rationale sound?	8	0	6
Is the proposal well planned and designed?	8	0	6
Is the proposal feasible?	4	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

- The reporter cell lines and expected improvements in photoreceptor differentiation from this pilot study will likely be useful tools for translating to clinical applications.
- The proposed tool is very medically relevant and translatable in the future.
- This is a highly-needed resource and the strategy is well designed.
- A detailed, well-justified optimization approach is included in the proposal.

Concerns

- While the proposal will tackle critical issues in improving differentiation of retinal progenitors and increasing yield of photoreceptor cells, there is limited novelty in proposed approaches, and the hypothesis is vague.

Additional Comments

- Would benefit from functional evaluation of cells in addition to marker expression.

Public Summary for DISC1-08692

Application #	DISC1-08692
Title (as written by the applicant)	Generation of vascularized cerebral motor cortex organoids for treatment of motor deficits after stroke.
Research Objective (as written by the applicant)	We will use our induced pluripotent stem cells to generate a 3D model of the human cortex that contains a capillary network. This 3D model may be used for transplantation to replace injured brain.
Impact (as written by the applicant)	Blood vessels inside the 3D reconstructions of the human cortex may greatly enhance the survival and growth of the graft so that they can be better used for transplantation in stroke patients.
Major Proposed Activities (as written by the applicant)	• Develop 3D model of human cortex in cell culture without capillary network. • Derive blood vessel wall progenitors from our induced pluripotent stem cell line. • Develop protocols to grow 3D models of the human cortex which contain a capillary network. • Transplant human cortical 3D models with and without capillary network into immuno-compromised mice to study their integration. • Transplant human cortical 3D models with and without capillary network into a rat stroke model to study their integration.
Statement of Benefit to California (as written by the applicant)	Stroke is a leading cause of morbidity and mortality and leads to high costs for the society. Recovery may take 2 years, but after this time the recovery reaches a plateau, and the patient is left behind with permanent deficits. We have successfully derived induced pluripotent stem cells and motor cortex cells from a State of California citizen. We will generate 3D models of the brain with a capillary network from this patient's cells in order to reverse paralysis after stroke in the future.
Funds Requested	$235,800
GWG Recommendation	***Tier 2 – Not recommended for funding.***

Final Score: 69

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.

Median	70
Standard Deviation	6
Highest	75
Lowest	50
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (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?	6	6	3
Is the rationale sound?	2	10	3
Is the proposal well planned and designed?	0	11	4
Is the proposal feasible?	0	9	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 proposal presents an important problem about which we know little in defining a successful therapy.
- The idea of vascularizing organoids is interesting.

Concerns

- Overall, the rationale is valuable and the use of organoids in stroke is interesting. However, the rigor in characterizing the cells that are going to be transplanted is lacking and no adequate stroke model that recapitulated the human situation the applicant present in the beginning of the application is proposed

- The proposed preclinical model experiments are very poorly defined, and there is no indication given of what outcomes will be considered sufficiently successful to move forward.
- There are concerns about cellular heterogeneity. The investigators fail to define what level of purity they can or are seeking to achieve in their differentiation paradigms
- The proposal has very questionable feasibility with respect to achieving vascularization. The invasion of angioblasts is not well-addressed experimentally.
- There is a very superficial consideration of concerns or potential pitfalls.
- The differentiation achieved does not seem convincing.

Additional Comments

- There is a general lack of care in defining how the research will progress from one stage to the next.

Public Summary for DISC1-08698

Application #	DISC1-08698
Title (as written by the applicant)	Targeting IGF1 signaling pathway to promote hematopoietic stem cell engraftments.
Research Objective (as written by the applicant)	To modify a key signaling pathway in human umbilical cord blood stem cells (UCB HSCs) in order to make them more amenable for transplantation in adult patients suffering from blood disorders.
Impact (as written by the applicant)	Making UCB HSCs more amenable for transplantation in adult recipients has the potential to save the lives of patients that have difficulty finding a bone marrow match.
Major Proposed Activities (as written by the applicant)	• To target a key pathway in UCB HSCs to determine if it increases their ability to engraft and regenerate the blood cells faster. • To identify the key gene and protein expression changes that occur in UCB HSCs when this key pathway is targeted.
Statement of Benefit to California (as written by the applicant)	UCB can be used as an alternative to bone marrow HSCs due to ease of collection and less requirements for compatibility between donors and recipients. The weakness of UCB is the limited numbers of HSCs, result in a prolonged recovery period. Our study will help mitigate this weakness and decrease the reliance of finding a bone marrow match. This is especially important for patients of minority or mixed ethnic backgrounds who are unable to find matching donors due to their rare genetic makeups.
Funds Requested	$234,270
GWG Recommendation	***Tier 2 - Not recommended for funding.***

Final Score: 76

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.

Median	75
Standard Deviation	2
Highest	80
Lowest	75
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (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?	5	4	6
Is the rationale sound?	3	5	7
Is the proposal well planned and designed?	3	4	8
Is the proposal feasible?	3	2	10

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 is logical and contains an interesting approach.
- The objective of the proposal is increased hematopoietic stem cell engraftment and faster immune system reconstitution after transplantation.
- There is a strong next step: adapt the human umbilical cord blood (UCB) treatment protocol into a current Good Manufacturing Practice protocol in order to conduct clinical trials with patients that require UCB transplantation due to the lack of a matched bone marrow donor.

Concerns

- The work is solid, and provides the logical next steps; however, there is a concern that the analysis will be difficult to achieve and more effective measurements of HSC function would be beneficial.
- There is some concern on possible off target effects and how this would be investigated.

Additional Comments

- Proposal is strong, all elements are positive, and while these are strengths for most funding mechanisms, the proposal seems a bit incremental for this funding mechanism.

Public Summary for DISC1-08711

Application #	DISC1-08711
Title (as written by the applicant)	Bone-healing cartilage derived from human pluripotent cells for the repair of large-scale bone injuries.
Research Objective (as written by the applicant)	To test that highly purified chondroprogenitors derived from pluripotent stem cells can induce bone formation and be used to repair large-scale bone defects in animal models.
Impact (as written by the applicant)	In the future, this method to generate purified chondroprogenitors could be used for the repair of a wide variety of bone injuries in humans (ie., long bone, skull, spine, jaw).
Major Proposed Activities (as written by the applicant)	• Optimizing the generation of bone using human chondroprogenitors derived from pluripotent stem cells. • Testing the ability of purified human chondroprogenitors to contribute to new bone in a large-scale bone repair assay.
Statement of Benefit to California (as written by the applicant)	The state of California has a large population of workers who suffer from skeletal injuries. These injuries cause pain, stress, and economic hardship. The studies proposed here which involve a new strategy--to repair bone by using stem cells that have been converted to cartilage -- could result in significantly better treatments for bone injuries. These treatments could better restore skeletal function and ultimately improve patient outcome.
Funds Requested	$250,200
GWG Recommendation	***Tier 2 - Not recommended for funding.***

Final Score: 82

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.

Median	80
Standard Deviation	6
Highest	95
Lowest	75
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	7
Tier 2 (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?	7	4	4
Is the rationale sound?	8	3	4
Is the proposal well planned and designed?	7	1	7
Is the proposal feasible?	6	1	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 investigators propose a highly innovative idea to use pluripotent stem cell (PSC)-derived chondrocyte progenitors in the healing of large bone defects. This notion has a strong basis in wound repair.
- The experiments are well-designed to test specific cell populations in a novel model of bone repair.
- It is clear that the team can generate highly purified human chondroprogenitors from PSCs. Aim 1 will investigate improving this process by investigating if stimulating key signaling pathways will create “better” chondrocytes.

Concerns

- Completion of Aim 1 will result in an incremental step in the overall question of how to heal large bone breaks.

Additional Comments

- The investigators provide extremely strong preliminary data. Some reviewers considered this preliminary data as a negative, potentially indicating that this project was too advanced for an Inception Award and suggesting it would be more appropriate for a Quest proposal.

- The entire goal of the proposal could be directly addressed by examining the periosteum (this would not be a stem cell-based question).

Public Summary for DISC1-08720

Application #	DISC1-08720
Title (as written by the applicant)	Development of Liver Organoids from iPSCs to Treat Hemophilia A
Research Objective (as written by the applicant)	To develop a novel autologous cell therapy using organoids derived from hemophilia A patient specific iPSCs to express F8 and to functionally correct hemophilia A, a bleeding disorder.
Impact (as written by the applicant)	Our novel approach may lead to a cure for hemophilia A, significantly reduce the economic burdens with the disease and can also be applied to treat other genetic deficiencies.
Major Proposed Activities (as written by the applicant)	• Differentiate hepatocyte and endothelial progenitor cells from hemophilia A patient specific iPSCs and express F8 in these cells using lentiviral vectors encoding the F8 gene. • Generate liver organoids from liver/endothelial progenitor cells in vitro and transplant these organoids into an immunodeficient mouse model and the hemophilia A mouse model. • Evaluate the long-term engraftment and the F8 expression of the organoids in immunodeficient mice (NOD/SCID/IL2Rg-/-) by IVIS imaging, histological analysis, immunostaining, RT-PCR and ELISA. • Evaluate the therapeutic effects of the organoids in hemophilia A mice by assessing the activity of FVIII and tail-clip bleeding challenge in these mice comparing to the mice without the organoids.
Statement of Benefit to California (as written by the applicant)	Hemophilia A is a life-threatening bleeding disorder and affects 1 in 5000 males. California has 38.8 million residents, so about 3800 people in California could have hemophilia A. Recombinant FVIII can treat but not cure hemophilia A. The median cost of treatment is $98,334 a year and is a lifelong expense. Our novel organoid approach for delivering therapeutic FVIII proteins may lead to a cure of hemophilia A and significantly reduce the economic burdens to the patient family and the society.
Funds Requested	$235,800
GWG Recommendation	***Tier 2 – Not recommended for funding.***

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.

Median	80
Standard Deviation	6
Highest	88
Lowest	70
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	4
Tier 2 (1-84): Not recommended for funding	11

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	2	5
Is the rationale sound?	5	3	7
Is the proposal well planned and designed?	4	5	6
Is the proposal feasible?	1	6	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

- Liver organoids will be made from induced pluripotent stem cells (iPSCs) as a novel vehicle to deliver FVIII to functionally correct hemophilia A in animal models. This study is the first test of using organoids to treat hemophilia A.
- Preliminary data show growth and differentiation of liver organoids generated with iPSC-derived hepatocyte and endothelial progenitor cells and lentiviral vector that expresses the F8 gene.
- The applicant institution and its resources will facilitate direct translation of the studies into clinical trials once efficacy and safety are demonstrated in small and large preclinical models.

- The proposal aims at taking a step towards a patient-specific treatment and eventual cure of Hemophilia A using iPSCs derived from patients. Achieving sustained *in vivo* production of the required FVIII is interesting and has translational relevance.

- High risk, high reward. If natural production of missing factors can be made routine for hemophilia, diabetes, and other disorders, a whole set of clinical therapies will be transformed.

Concerns

- A scale-up for the production of liver organoids is proposed, but it is unclear what this means and what they would be used for.

- It is worrying that the Principal Investigator (PI) states that they do "not anticipate any technical difficulties in the proposed studies, because we are experienced in all the methodologies proposed".

- An optimization of the conditions to transplant aggregated organoids is proposed but no details are provided. This step is essential and the current proposal would be improved with the addition of experiments that would address how organoid stability/size could be improved. The next step is not addressed in detail.

Additional Comments

- The chances of an eventual translation to a product are limited. The proposal stops at the evaluation of therapeutic effects of engrafted liver organoids in mice, but translation of this to humans seems remote, in particular given that there are alternative approaches, e.g. AAV-mediated gene therapies, which are at the stage of clinical trials.

Public Summary for DISC1-08721

Application #	DISC1-08721
Title (as written by the applicant)	Deciphering the genetic mechanisms of Parkinson's diseases for improved safety of stem cell based therapy.
Research Objective (as written by the applicant)	Identify functional genetic variations that predispose people to Parkinson's disease (PD), and consequently can be used for biomarkers to screening stem cells before PD stem cell replacement therapy.
Impact (as written by the applicant)	Ability to interpret the functions of common genetic variation in Parkinson's patients will have profound impact on improving the long term safety of the cell transplantation treatment.
Major Proposed Activities (as written by the applicant)	• Comprehensively test thousands common genetic variations enriched in PD patients in induced pluripotent stem cell-derived dopaminergic neurons utilizing novel functional genomic approaches. • Investigate the molecular mechanisms and validate the functions of functional variations, and generate a panel of biomarkers that should be screened and corrected before cell transplantation.
Statement of Benefit to California (as written by the applicant)	Parkinson's disease (PD) affects approximately 1 in 100 people over the age of 60. PD is primarily caused by the progressive loss of dopamine (DA) neurons in the midbrain and with no cure. Using patient iPSCs derived DA neurons for Parkinson therapy is one potential way of treating PD. Identification of genetic variations predispose patients to PD will shed light on how to screening and correcting the DNA sequences from PD patients for the long term safety of the stem cell replacement therapy.
Funds Requested	$238,500
GWG Recommendation	***Tier 2 – Not recommended for funding.***

Final Score: Below 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.

Median	---
Standard Deviation	---
Highest	---
Lowest	---
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (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?	4	6	4
Is the rationale sound?	0	13	1
Is the proposal well planned and designed?	0	12	2
Is the proposal feasible?	0	7	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

- This is good first step in an important area.
- Two clear specific aims that might provide some basic insights into join-coding single nucleotide polymorphisms (SNPs) and their impact on gene regulation with a possible link to PD.

Concerns

- The applicant has conceptually tied the program to the development of a stem cell-based brain repair therapy for PD. This is not where the primary value of the research program lies since correction of “genetic risk” for PD is not likely to significantly impact the 10-20 year post-surgery outcome of a transplantation therapy.

- The applicant lacks Parkinson's disease expertise in the team. While the applicant is very strong in epigenetics and stem cells, this shortcoming is a major concern and is reflected in the current plans for experiments.
- The genomic and genetic linkage bioinformatics is unclear. As described, the concern is that no causative variants will be identified in Aim 1.
- It is unclear how the variants will be assayed in the iPS cells in Aim 2.
- 75% effort of a first-year postdoc without prior experience in human linkage analysis is insufficient for the scope of the bioinformatics required.
- There is some concern about Aim 1 not being feasible; subsequent aims are affected.
- Focus on mid brain dopaminergic neurons are a concern as other populations might influence PD.
- The kind of candidate genes that are expected to be discovered are not addressed.
- The focus on the effects of the regulatory variants only in midbrain dopamine neurons is a shortcoming. Additional cells are affected in PD. With respect to Aim 2.1.2, there is no hint what this target gene could be, or what category of genes it could be related to. Would a gene that had a broader function (also in other cells) be disqualified?

Additional Comments

- No relevant additional comments were expressed by the GWG.

Public Summary for DISC1-08723

Application #	DISC1-08723
Title (as written by the applicant)	iPS-Interneuron Transplantation for Neural Repair after Stroke.
Research Objective (as written by the applicant)	To determine if transplantation of iPS-interneurons cells (iPS-3i cells) enhances functional recovery in stroke.
Impact (as written by the applicant)	Successful completion of the proposed studies will develop a brain repair therapy for stroke, an unmet clinical need with significant impact on society.
Major Proposed Activities (as written by the applicant)	• To determine the recovery effect of transplantation of iPS-3i cells in the mouse at sub-acute (7 days after stroke) and chronic (21 days) points, using measures that mimic human functional recovery. • To determine the integration and circuit properties of transplanted iPS-3i cells in stroke at sub-acute and chronic time points using anatomical and optogenetic circuit mapping.
Statement of Benefit to California (as written by the applicant)	Stroke is the leading cause of adult disability. There is no medical therapy that promotes recovery in this disease. This research will test the effect of a new cellular transplant strategy to promote recovery in stroke, using induced pluripotent stem cells that have been differentiated into interneurons. These cells have markedly improved survival, migration and engraftment than previous stem cell approaches in stroke, and induce a form of plasticity that mimics the limited recovery in stroke.
Funds Requested	$229,396
GWG Recommendation	***Tier 1 - Exceptional merit and warrants funding, if funds are available.***

Final Score: 95

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.

Median	95
Standard Deviation	2
Highest	97
Lowest	90
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	15
Tier 2 (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	3
Is the rationale sound?	12	0	3
Is the proposal well planned and designed?	13	0	2
Is the proposal feasible?	12	0	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

- This is a wonderful application with a strong approach and a strong team. This work needs to be done, and all the caveats have been acknowledged.
- Beautifully and thoughtfully written application taking virtually all concerns/pitfalls into account. There is high feasibility.
- The approach is strongly quantitative and analytic.

- The proposal contains a novel ideal and describes a very exciting approach to a significant problem.
- Different possibilities for mode of action are considered ranging from cell integration to indirect effects.
- There is a go/no-go decision based on results from Aim 1. The protocol will be suspended if no improvement in function can be observed.

Concerns

- No significant concerns were expressed by the GWG.

Additional Comments

- Cell retention will likely be enhanced cell retention by co-administration of hydrogel.
- Both the acute and chronic models of ischemic brain injury with regulatory relevance are a strength. For small molecule development, the relevance for cell therapeutics needs to be confirmed.

Public Summary for DISC1-08727

Application #	DISC1-08727
Title (as written by the applicant)	Adipose-derived native perivascular mesenchymal stem cells for treatment of ovarian failure.
Research Objective (as written by the applicant)	We will determine if transplantation of native pericytes to the ovary can restore the reproductive endocrine and ovarian function in chemotherapy damaged ovaries.
Impact (as written by the applicant)	This therapy has the potential as a treatment option for young cancer survivors by regenerating the patient's endocrine function for improved long-term health and quality of life.
Major Proposed Activities (as written by the applicant)	• Isolation of native pericytes from human adipose tissue using FC sorting. • Transplantation into chemotherapy treated mice. • Measure the ability of these cells to regenerate endocrine and reproductive function; immunohistochemistry, gene expression, and direct hormone assays. • Immunohistochemistry to define dynamics and location of pericytes within ovaries of mice and humans; fixed, paraffin-mounted tissue sections.
Statement of Benefit to California (as written by the applicant)	Chemotherapy and radiation treatments frequently disrupt the reproductive endocrine axis causing damage to ovaries. This damage causes premature ovarian failure in cancer survivors with resulting health effects including osteoporosis, cardiovascular disease and infertility. Autologous transplant of perivascular stem cells into the ovary has the potential to regenerate tissues and revive natural steroid hormone levels to improved health and quality of life for young cancer survivors.
Funds Requested	$250,200
GWG Recommendation	***Tier 2 – Not recommended for funding.***

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.

Median	65
Standard Deviation	3
Highest	70
Lowest	60
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (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?	5	3	7
Is the rationale sound?	1	7	7
Is the proposal well planned and designed?	0	8	7
Is the proposal feasible?	2	2	11

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 significance of the proposal lies in importance of clinical problems related to infertility and endocrine disruptions in cancer survivors post chemo and radiation therapy.

Concerns

- The rationale is weak as it is based on previous studies that are highly controversial and are not independently reproduced.
- The scientific rationale of why using pericytes are the most suitable cell type over any other cell type of the human body is not clear.

- There is no convincing hypothesis or preliminary data supporting that adipose-derived native perivascular mesenchymal stem cells can be reprogrammed into becoming estrogen producing theca cells.
- There is a risk of cancer recurrence after autologous transplantation. An alternative approach of transplanting cryopreserved ovarian tissues has been already clinically tested in humans.
- There are concerns with the statistical power of experiments proposed in this proposal.

Additional Comments

- It would have been more informative, for the histological and gene expression profiles, to inject cells in one ovary and saline in the other ovary of the same animal. It is also important to consider using other cells as a control as well, such as fibroblasts.

Public Summary for DISC1-08731

Application #	DISC1-08731
Title (as written by the applicant)	Autologous iPSC-based therapy for radiation induced bladder injury.
Research Objective (as written by the applicant)	To explore if iPSC-based therapy can prevent bladder damage due to radiation therapy, thereby limiting the unintended consequences of treatments for prostate, gynecologic and colorectal cancers.
Impact (as written by the applicant)	This therapy impacts cancer survivors by preventing the permanent debilitating urinary symptoms due to radiation therapy. Currently there are no therapies to prevent radiation bladder damage.
Major Proposed Activities (as written by the applicant)	• Optimize and characterize a chronic radiation cystitis rat model (6 months) using two radiation doses (25 Gy and 35 Gy) to establish time course and baseline changes in inflammatory parameters. • Inject human iPSC-derived pSMCs into the bladder of rat model after radiation to evaluate the effect of pSMC on bladder function and scarring/fibrosis.
Statement of Benefit to California (as written by the applicant)	Pelvic cancers such as prostate, gynecologic, and colorectal cancers are often treated with radiation therapy(RT). Roughly 54,000 new cases are diagnosed annually in California. Despite RT advances, unintended chronic bladder damage cause debilitating bladder symptoms in up to 10% of patients. Therapies to ameliorate these symptoms are lacking and risky. We propose a stem-cell-based therapy. Our treatment could improve the post-cancer recovery of Californians who currently suffer needlessly.
Funds Requested	$237,564
GWG Recommendation	***Tier 1 – Exceptional merit and warrants funding, if funds are available.***

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.

Median	90
Standard Deviation	2
Highest	95
Lowest	85
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	15
Tier 2 (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?	11	1	3
Is the rationale sound?	12	1	2
Is the proposal well planned and designed?	12	1	2
Is the proposal feasible?	11	0	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

- This is strong grant with potential high medical significance and an important unmet medical need.
- This is a well rationalized application with a clearly defined approach.
- The application builds on a previously funded grant and demonstrates productivity.
- Preliminary data is very strong and shows that the team can create large numbers of smooth muscle cells from patient derived induced pluripotent stem cells.

- Damage to the urinary track is not usually reversible. As a result, most treatments are geared towards managing the symptoms and not treating the underlying cause.

Concerns

- No significant concerns were expressed by the GWG.

Additional Comments

- Conducting the work in a cancer bearing model would have been perhaps even more relevant.

Public Summary for DISC1-08733

Application #	DISC1-08733
Title (as written by the applicant)	Interleukin-10 producing Mesenchymal Stem Cells for the treatment of post-traumatic osteoarthritis.
Research Objective (as written by the applicant)	The goal of this proposal is to test in a relevant animal model of post-traumatic osteoarthritis, the efficacy of Mesenchymal Stem Cells (MSCs) over-expressing Interleukin 10 and test mechanisms of action.
Impact (as written by the applicant)	Our approach combines previous efforts with MSC and anti-inflammatory cytokines to treat Osteoarthritis. If successful, we may have developed a new therapeutic agent for a largely unmet clinical need.
Major Proposed Activities (as written by the applicant)	• Evaluate the effect of MSC/IL-10 on inflammatory signals, measured within the first 3 days after non-invasive ligament rupture in mice. • Evaluate the effect of MSC/IL-10 on fibrosis, measured seven days after ligament rupture in mice. • Evaluate the effect of MSC/IL-10 on matrix metalloproteinases activity measured by luminescence weekly, for up to 28 days. • 28 days after ligament rupture, test the effect of MSC/IL-10 to restore hallmarks of PTOA (damage in bone and cartilage, among others). • Measure presence of injected cells by luminescence weekly, for up to 8 weeks. • At end point, evaluate cell distribution of MSC/IL-10 within the joint.
Statement of Benefit to California (as written by the applicant)	In California, as in the rest of the world, osteoarthritis is an extremely common condition. In addition to the economic benefit of possibly being the developers of a new therapy for this immensely unmet medical need, to have a treatment for this condition is simply unmeasurable.
Funds Requested	$235,588
GWG Recommendation	***Tier 2 – Not recommended for funding.***

Final Score: 74

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.

Median	75
Standard Deviation	5
Highest	85
Lowest	70
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	1
Tier 2 (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?	2	2	11
Is the proposal well planned and designed?	2	8	5
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 significance of this problem is huge and the combination of MSC with IL10 is great.
- The preliminary data is compelling.

Concerns

- The potential pitfalls are not specifically addressed.

- The proposal ends with the statement “Each specific aim is remarkably independent from one another…….”, which is a major issue. It is unclear how the data obtained in the two aims complement each other.

- In Aim 1, a particular mouse model will be used, which can be used to induce ACL tears and OA. However, in Aim 2, the SCID model will be used to determine how many MSCs are retained after injection. It will be impossible to correlate data between the two Aims. The SCID model is proposed in Aim 2 because OA is not easily modeled in this genetic background. It is unclear what use the data obtained in Aim 2 will be.

Additional Comments

- MSCs will be injected “minutes” after ACL rupture. A discussion on how feasible this will be in clinical trials needs to be included.

Public Summary for DISC1-08737

Application #	DISC1-08737
Title (as written by the applicant)	New Methods for the Chemical Expansion of Hematopoietic Stem and Progenitor Cells.
Research Objective (as written by the applicant)	We will develop a new agent that can increase the production of hematopoietic stem and progenitor cells and determine how the compound functions.
Impact (as written by the applicant)	We aim to develop a method to achieve the highest fold expansion of hematopoietic stem cells from a single unit of cord blood achieved to date increasing the supply of these clinically relevant cells.
Major Proposed Activities (as written by the applicant)	• We will identify the biological target(s) of our novel compound that promotes expansion and inhibit differentiation. • We will develop conditions using existing agents for expansion in combination with our new compound to maximize the expansion of hematopoietic stem and progenitor cells from cord blood.
Statement of Benefit to California (as written by the applicant)	We aim to develop a cost effective, cryopreserved source of hematopoietic stem cells by providing an expansive source of produced through the expansion of cord blood using well defined agents. This would provide a widely available, economically adjusted product for widespread use in California and beyond.
Funds Requested	$232,200
GWG Recommendation	***Tier 1 – Exceptional merit and warrants funding, if funds are available.***

Final Score: 86

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.

Median	85
Standard Deviation	2
Highest	90
Lowest	85
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	15
Tier 2 (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?	10	1	4
Is the rationale sound?	9	1	5
Is the proposal well planned and designed?	4	3	8
Is the proposal feasible?	6	1	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 novelty of the compound's action is excellent.
- This is a clear proposal with a possibly valuable compound.
- The proposed work is highly significant, and the test of the compound is very much worthwhile.

Concerns

- The PI could have been clearer in the experimental approaches, and whether the expanded hematopoietic stem cells will be tested *in vivo.*

Additional Comments

- No relevant comments were expressed by the GWG.

Public Summary for DISC1-08750

Application #	DISC1-08750
Title (as written by the applicant)	Curing bladder cancer by replacing corrupted urothelium with differentiated hES cells.
Research Objective (as written by the applicant)	The goal of the proposed research is to use human embryonic stem cells to generate bladder epithelial progenitor cells that can be used to replace a cancerous bladder epithelium in vivo.
Impact (as written by the applicant)	The long-term goal of the proposed research is to cure bladder cancer. Successful completion of this work may indicate that transplantation of differentiated pluripotent stem cells is a feasible cure.
Major Proposed Activities (as written by the applicant)	• We seek to differentiate human embryonic stem cells into bladder epithelial progenitors. To this end, we will test stem cell culture conditions that promote the bladder epithelial progenitor state. • Using a mouse model for bladder cancer, we will determine whether transplantation of differentiated human embryonic stem cells can functionally replace a cancerous bladder epithelium.
Statement of Benefit to California (as written by the applicant)	The long-term goal of the proposed research is to develop a cure for bladder cancer, one of the most prevalent cancers worldwide. Muscle invasive bladder cancer (MIBC) is uniformly lethal if left untreated. Surgical removal of MIBC is frequently followed by recurrence and/or a dramatic reduction in quality of life. Moreover, bladder cancer is the most expensive cancer to treat per patient. A definitive cure for bladder cancer therefore would have wide-ranging positive impacts.
Funds Requested	$237,564
GWG Recommendation	***Tier 1 – Exceptional merit and warrant funding, if funds are available.***

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.

Median	86
Standard Deviation	6
Highest	100
Lowest	75
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	11
Tier 2 (1-84): Not recommended for funding	3

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?	9	3	3
Is the proposal well planned and designed?	7	2	6
Is the proposal feasible?	5	5	5

Reviewer

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

- This is a novel approach is to use human embryonic stem cells to generate bladder epithelial progenitor cells that can be used to replace a cancerous bladder epithelium *in vivo*. This is a high-risk project that would be difficult to fund by the usual NIH mechanisms.
- The careful experimentation, data collection and analysis could teach us much about this novel approach, even if these preliminary experiments "fail". Perhaps, organoids (harboring their own progenitor cell "niche"), would be better to transplant, or in combination with the pure population of progenitor cells.
- There is high risk, high reward with strong translational potential in this proposal.

- The overall rationale is exciting and the potential for advancing the field in a significant manner is very high.

Concerns

- There are weaknesses in identifying the path towards a functional bladder epithelium from their stem cells; there is a lack of a clear approach to obtain bladder epithelial progenitors.

- An objective of the approach is to prevent re-occurrence of the cancer. This requires that healthy cells will outgrow or inhibit the growth of left over cancer cells. While an *in vivo* approach is presented to test whether this will actually occur, there is no discussion of where the project will go should the cancer cells repopulate the ablated bladder.

Additional Comments

- This proposal is highly ambitious; either aim could be a proposal on its own.

- This project contains a high level of risk.
    - Will the basal muscle layers survive epithelial ablation and provide a niche in which the transplanted human embryonic stem cells can take hold, expand, establish healthy epithelium, and keep the cancer ever at bay?

    - Could cancer mutations in patients also be present in the muscle cell layer (or quiescent cancer cells hide out there), and after ablation, these cells transdifferentiate or activate to take over the denuded epithelial compartment?

- There is concern that even if the bladder epithelium is replaced from stem-cell-derived cells, that this may not be curative as recurrence of the cancer seems likely even after transplantation. There are also concerns that the cells produced may not be optimal. However, the overall idea is novel and of interest such that some findings regarding the transplantation of epithelial layers may be forthcoming.

Public Summary for DISC1-08766

Application #	DISC1-08766
Title (as written by the applicant)	Identification of novel targets through neurotransmitter regulation of neuronal differentiation translating to clinical applications in Parkinson's disease.
Research Objective (as written by the applicant)	The objective is the modeling the brain milieu to understand receptor pharmacology of neuronal differentiation for PD patient iPSC-derived neuronal cultures to identify novel therapeutic targets.
Impact (as written by the applicant)	High-throughput robust screening tools for neurodegenerative disorders are urgently needed for compound screening and target validation which will be the main deliverable of this study.
Major Proposed Activities (as written by the applicant)	• Survival and expansion of cells will be measured under all conditions of neurotransmitter exposure. • Efficiency of neuronal differentiation will be measured with specific neuronal and glial protein markers under all neurotransmitter conditions. • Expression markers of pluripotency, neural induction, and mature neuronal and glial markers are measured under all neurotransmitter conditions. • Electrical activity of generated neurons will be performed on optimized culture conditions with highest change in differentiation efficiency under all neurotransmitter conditions. • Alpha-synuclein staining with different antibodies is used to assess changes in expression, aggregation and pathological forms of alpha-synuclein.
Statement of Benefit to California (as written by the applicant)	Parkinson's disease (PD) is a chronic progressive neurodegenerative disease with 1% of people over the age of 60 affected. It is estimated that this number will double by the year 2030 and with this increases the burden and health care cost which is estimated with up to $25 billion per year in the US. Current therapies are only symptomatic and don't stop disease progression. Finding better treatments for PD will not only benefit the people of California, but patients with PD world-wide.
Funds Requested	$255,420
GWG Recommendation	***Tier 2 - Not recommended for funding.***

Final Score: Below 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.

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

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (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?	2	6	7
Is the rationale sound?	1	10	4
Is the proposal well planned and designed?	0	9	6
Is the proposal feasible?	0	4	11

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

- Understanding the role of neurotransmitters in neuronal development is important.

Concerns

- The proposal has a limited scope of investigation; factors are not necessarily conjoint temporally during development.
- There is limited relevance to disease process.
- *In vitro* cultures do not include glia or other relevant cell types (which might influence or be influenced by neurotransmitter levels).

- The information provided is so minimal that the project is entirely speculative.
- How the project would move beyond the initial stages is not appropriately defined.
- Very few samples are being tested, and only one (or a few) particular combination of neurotransmitters, dose, and frequency is being tested.
- It is not clear the *in vitro* experiments recapitulate anything like what might occur *in vivo*.

Additional Comments

- No relevant comments were expressed by the GWG.

Public Summary for DISC1-08776

Application #	DISC1-08776
Title (as written by the applicant)	Genome editing for causation and reversion of MPN-associated mutations in human hematopoietic stem cells
Research Objective (as written by the applicant)	Use gene editing to create tools for the study of mechanisms by which patient-observed mutations lead to myeloproliferative neoplasms (MPN).
Impact (as written by the applicant)	Editing reagents will yield new insight into how acquired MPN-associated mutations cause disease by overproduction of various cell types and pave the way for gene editing therapies to reverse MPNs.
Major Proposed Activities (as written by the applicant)	• Develop tools to enable the study of MPN-associated mutations at endogenous loci. • Create isogenic human cell lines harboring MPN-associated mutations and introduce mutations to primary human CD34+ HSCs.
Statement of Benefit to California (as written by the applicant)	The research described in this proposal will both yield new information to the MPN family of hematopoietic disorders and broadly enable the creation and reversion of mutations in hematopoietic stem cells. New understanding of MPNs could lead to improved drugs to treat these disorders. Methods to perform gene editing in hematopoietic stem cells could be transformative for the treatment of inherited and acquired blood diseases, potentially allowing gene editing therapies to cure such disorders.
Funds Requested	$235,800
GWG Recommendation	***Tier 1 – Exceptional merit and warrants funding, if funds are available.***

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.

Median	85
Standard Deviation	3
Highest	90
Lowest	80
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	11
Tier 2 (1-84): Not recommended for funding	4

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?	11	1	3
Is the proposal well planned and designed?	7	1	7
Is the proposal feasible?	9	0	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

- A solid proposal describing a very interesting technology that provides an important set of tools for study of a defined set of disease mutations. This technology can impact the study of disease biology and therapeutic target identification.
- The proposed experiments will produce reagents that will be useful for studying, *in vitro*, myeloproliferative neoplasms (MPN) diseases at a future date.
- The targeting of hematopoietic stem cells, particularly the generation of MPN mutations in the three genes described in the proposal, is an exciting and necessary step in the investigation of these genes.

- This proposal has a very strong and direct impact on research of MPNs with a clear path towards translation and is very suited to CIRM's mission.
- The genetic architecture of MPNs offers a really exciting (and somewhat unusual compared to other diseases and cancers) opportunity to examine a strongly oligogenic disease. Particularly interesting is that the major mutations are already known.

Concerns

- A minor concern is the somewhat vague description on the eventual use of the cells.
- There is no justification for pursuing these particular transmitters for *in vivo* conjunction.
- There are limited cellular constituents, like the lack of glia. The effects on neurotransmitters are well known but not considered here adequately.
- The proposal will validate tools to study MPN-associated mutations (Aim 1) and then create isogenic human cell lines that have MPN-mutations. However, the outcomes of these experiments are not described well, which is a major concern.

Additional Comments

- The grant reaches sort of a soft spot in its presentation towards the end, and so ends with a bit of a "thud" thereby diminishing excitement. In short, what assays will be used to study the cells once made? Even if this work is not planned in this funding cycle, you can attempt to be fairly specific. Otherwise reviewers are left wondering if these cells have any uses. Don't make the review panel infer the grant for you, even if it seems obvious to some.
- An obvious thing to do is to make induced pluripotent stem cells with these mutations for study. This might be so obvious that the grant is perhaps hardly "innovative". However, the importance of this step to MPN research is huge and should be taken.

Public Summary for DISC1-08777

Application #	DISC1-08777
Title (as written by the applicant)	Stem Cell Maintenance in Falconi Anemias by Pharmacologic Modulation of Aldehyde Metabolism
Research Objective (as written by the applicant)	To test the feasibility of pharmacologic activation of aldehyde dehydrogenase 2 (ALDH2) to decrease the aldehydic load in hematopoietic stem cells (HSC) from patients with Fanconi anemia (FA).
Impact (as written by the applicant)	Reducing aldehyde load will reduce genotoxic DNA damage and decrease the risk of aplastic anemia, leukemia and solid tumors in FA patients.
Major Proposed Activities (as written by the applicant)	• Determine whether pharmacologic activation of ALDH can rescue FA stem cells in vivo using murine models of FA. • Determine whether small molecule activators of ALDH2, Alda-1 and Alda-89, alter normal human HSC behavior in vitro and in chimeric mice.
Statement of Benefit to California (as written by the applicant)	ALDH activators reduce DNA damage inducing aldehydes in hematopoietic stem cells (HSC). Using novel ALDH activators, we will develop pre-clinical data that could reduce HSC damage, marrow failure and cancer, and radically improve outcome in Fanconi anemia (FA) patients. While FA is rare, findings have relevance to patients with a common ALDH2 gene mutation (ALDH2*2). This work will help refine key HSC protective mechanisms and help maintain California's lead position in Stem Cell research.
Funds Requested	$237,564
GWG Recommendation	***Tier 2 – Not recommended for funding.***

Final Score: 81

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.

Median	80
Standard Deviation	2
Highest	85
Lowest	80
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	3
Tier 2 (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?	11	0	4
Is the rationale sound?	7	1	7
Is the proposal well planned and designed?	1	5	9
Is the proposal feasible?	3	1	11

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 is highly translational.
- The experiments are well designed.
- This may be a new problem that was not appreciated previously.

Concerns

- There are some concerns about the lack of mechanistic investigations.
- The duration of treatment is of some concern.
- Using HSCs from patients with Fanconi Anemias (FA) would help.
- Mouse model does not adequately recapitulate human condition.

Additional Comments

- Modulating aldehyde levels may affect the propensity to progress to leukemia in FA patients.
- The idea is good, but further refinement of the research strategy is warranted.

Public Summary for DISC1-08782

Application #	DISC1-08782
Title (as written by the applicant)	Transplantation of GDNF-expressing neural progenitor cells to treat repeat mild/moderate traumatic brain injury
Research Objective (as written by the applicant)	To determine the potential of GDNF-expressing neural progenitor cells to provide significant therapeutic benefits in a rat model of TBI so that we may translate this strategy to the clinic.
Impact (as written by the applicant)	If successful, this strategy will have a considerable impact on clinical research in the field of TBI and could provide a breakthrough in treating TBI patients.
Major Proposed Activities (as written by the applicant)	• To understand the mechanisms associated with repeat mild and moderate TBI using a rat model. • To test whether the transplantation of GDNF-expressing human neural progenitor cells into the brain of injured rats can ameliorate the effects of repeat traumatic brain injury.
Statement of Benefit to California (as written by the applicant)	While this research will impact California citizens in general, it will have a particular impact on California professional sports and California military personnel. Head-injured athletes and veterans commonly suffer long-term, life-changing challenges. If the transplantation of stem cells into the brains of rats suffering from TBI is therapeutically successful, we will be closer to a clinical TBI treatment that can reduce the burden of this devastating condition on the state of California.
Funds Requested	$241,992
GWG Recommendation	***Tier 2 – Not recommended for funding.***

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.

Median	60
Standard Deviation	1
Highest	65
Lowest	60
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (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?	3	9	2
Is the rationale sound?	0	10	4
Is the proposal well planned and designed?	0	9	5
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

- No relevant strengths were expressed by the GWG.

Concerns

- The study plan and discussion of potential pitfalls are in general very superficial.
- The model is poorly described. Is there a skull fracture, a rotation element, white matter involvement, etc.?
- The rationale is underdeveloped, and the logic of the transplantation site is not clear.

- Cells are available, but they do not show supporting data. It is impossible to tell whether there is a likelihood of benefit.

Additional Comments

- The distributed nature of the injury makes it necessary to have a rationale for putting cells in particular locations, but such a rationale is not provided.

Public Summary for DISC1-08784

Application #	DISC1-08784
Title (as written by the applicant)	Establishment of human cancer stem cell lines from patients for eliminating the root of cancer relapse and metastasis
Research Objective (as written by the applicant)	Establishment of human cancer stem cell lines with epithelia, glial and mesenchymal types from patients for developing novel therapeutics to eliminate the root of cancer relapse and metastasis
Impact (as written by the applicant)	Providing an excellent opportunity to determine the mechanisms of tumorigenesis and cancer development, and to develop novel and effective therapeutics to eliminate cancer stem cells in cancer therapy
Major Proposed Activities (as written by the applicant)	• Establishing primary patient disease xenografts (PDX) of liver, pancreatic and breast cancers, sarcomas and glioblastomas in mice with the tumor tissues of patients. • Establishing secondary PDX tumors of five types of human cancers/tumors in mice employing primary PDX tumors. • Isolation and culture of cancer stem cells from PDX tumors of five human cancers/tumors. • Characterization of cultured cancer stem cells of five human cancers/tumors. • Validation of established cancer stem cells by forming the tumors in mice which are injected with established specific cancer stem cells. • Characterization of cancer stem cell-derived tumors and comparison with those of PDX tumors.
Statement of Benefit to California (as written by the applicant)	Over 90% of cancer death is associated with relapse and metastasis which are caused by cancer stem cells (CSC), established CSC lines from patients will provide better understanding the mechanisms of CSCs in cancer pathogenesis and allow to develop effective therapeutics to CSCs, the outcome will ultimately improve survival and quality of life of California's patients with cancers, and boost California's biotechnological and pharmaceutical industry on therapeutics address to unmet medical needs.
Funds Requested	$235,800
GWG Recommendation	***Tier 2 – Not recommended for funding.***

Final Score: Below 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.

Median	---
Standard Deviation	---
Highest	---
Lowest	---
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (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?	5	6	3
Is the rationale sound?	0	8	6
Is the proposal well planned and designed?	0	9	5
Is the proposal feasible?	0	12	2

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 identification and specific targeting of cancer stem cells (CSCs) to eradicate cancer and prevent relapse is a strength.
- It is important to understand the biology of cancer stems cells.
- The general idea of isolating and characterizing CSCs from these major cancers is relevant and exciting.

Concerns

- The project is overly ambitious. The application does not provide sufficient assurance in the experimental design that it is feasible and would produce true representative CSCs from the respective cancers.
- The grant is too ambitious. Perhaps the applicant should focus on a single tumor.
- Impossibly ambitious - all of the following for 5 major cancers: The plan is to isolate and propagate patient-disease xenografts (PDX) (months 4-6), isolate and culture CSC from PDX (months 4-6), characterize cultured CSC (months 7-9), compare CSC-derived tumors with PDX tumors (months 9-12).
- The markers are not entirely appropriate, and the functional analysis is a weakness. For example, EpCAM is a marker of the transient amplifying population.

Additional Comments

- Characterization techniques need to be described specifically with consideration to the available budget. "Tumor tissues/cells or re-culture cells will be used to determine their phenotypes and gene expression patterns by flow cytometry, immunohistochemistry analysis, regular PCR and quantitative PCR, or microarray assay," is a great way to characterize cells, but details are needed to evaluate what specifically is going to be proposed.

Public Summary for DISC1-08789

Application #	DISC1-08789
Title (as written by the applicant)	Targeting cancer stem cells in an orthotopic patient-derived xenograft model of ovarian cancer
Research Objective (as written by the applicant)	We aim to use small RNAs, delivered to tumors by nanoparticles, to make ovarian cancer (OC) stem cells more drug sensitive, less invasive, and less likely to regrow tumors and metastasize.
Impact (as written by the applicant)	Completion of this project will provide evidence necessary to advance therapeutics to clinical trials for recurrent metastatic ovarian cancer, and will improve our understanding of cancer stem cells.
Major Proposed Activities (as written by the applicant)	• We will examine cancer stem cell regulation in ovarian cancer. Therapeutics for decreasing drug resistance, invasion, and self-renewal will be optimized in the lab. • We will test the ability of therapeutics to impact stem cells in our preclinical ovarian cancer model, using nanoparticles for delivery of the small RNAs to tumors.
Statement of Benefit to California (as written by the applicant)	In California, there were 2,479 ovarian cancer diagnoses, and 1,515 deaths, in 2012, a higher incidence rate than in the US as a whole. Over 70% of OC patients' cancer will recur, and only 15-30% of recurrent OC responds to treatment. Completion of studies outlined here would progress therapeutics toward clinical trials for patients with recurrent metastatic OC. A plausible next step would be development of this stem cell-based therapeutic candidate under a CIRM 2.0 Translational award.
Funds Requested	$176,535
GWG Recommendation	***Tier 2 – Not recommended for funding.***

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.

Median	85
Standard Deviation	5
Highest	90
Lowest	72
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	8
Tier 2 (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?	11	1	3
Is the rationale sound?	7	3	5
Is the proposal well planned and designed?	6	2	7
Is the proposal feasible?	3	3	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

- The proposal represents a significant medical need and is an exciting idea.
- There is an element of high risk, high reward – the perfect balance for this funding mechanism.
- Although the proposal is overly ambitious, even partial progress would be worth the modest funding offered by the mechanism.
- This is a strong team with rising talents and a good publication record.

- Studying the role of endothelial to mesenchymal transition (EMT) as it affects cancer stem cell transitions is of good interest

Concerns

- This is an overambitious proposal, which cannot be completed in one year.
- There are concerns about heterogeneity of the cancer stem cells.
- There are some concerns about low specificity of nanoparticle approaches.

Additional Comments

- It is uncertain that the investigators fully appreciated the heterogeneity of ovarian cancers, which may mean the markers and the targeted pathways may not be generalizable across many tumors.

Public Summary for DISC1-08790

Application # (as written by the applicant)	**DISC1-08790**
Title (as written by the applicant)	Targeting progenitors in scar tissue to reduce chronic scar burden
Research Objective (as written by the applicant)	Develop novel strategies to treat heart scars by targeting progenitors that replenish scars
Impact (as written by the applicant)	There currently is no therapy for treating scar tissue in the heart or any other organ. Our proposal would lead to the development of targeted approaches to reduce scar burden.
Major Proposed Activities (as written by the applicant)	• Identify progenitors in scar tissue (murine and human) that have the ability to self renew and replenish scars. • Determine dynamics of scar replenishment by scar progenitors. • Antigenic and functional characterization of progenitors in human and murine scar tissue. • Creating monoclonal antibodies to target scar progenitors. • To determine whether monoclonal antibodies can be used in vivo to target progenitors in scar to disrupt scar replenishment and reduce chronic scar burden.
Statement of Benefit to California (as written by the applicant)	Every 30 seconds, someone in the United States including California suffers a heart attack and lost heart muscle is replaced by scar tissue. Scar tissue is irreversible and an independent predictor of mortality in patients with heart disease. Currently no therapies exist to reverse or retard scarring. In this proposal, we outline a novel therapeutic strategy to decrease chronic scar burden in the heart by targeting progenitor cells in scar tissue that self renew and replenish heart scars.
Funds Requested	$230,400
GWG Recommendation	***Tier 1 – Exceptional merit and warrants funding, if funds are available.***

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.

Median	90
Standard Deviation	2
Highest	92
Lowest	85
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	14
Tier 2 (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?	13	1	0
Is the rationale sound?	11	1	2
Is the proposal well planned and designed?	10	1	3
Is the proposal feasible?	10	0	4

Reviewer

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 idea that a scar is a dynamic tissue with its own stem cells is very novel. The implications for scar tissue biology would be very significant.
- Reducing scar size has immense therapeutic potential.
- The preliminary data is excellent and supports the core hypothesis.
- The experiments are well designed, and the limitations are well addressed.

- The proposal captures the spirit of the Program Announcement.

Concerns

- The strategy to kill human progenitors in the heart needs to be work out in more detail. An antibody alone will not kill the cells.
- Finding a specific epitope on the putative progenitor will be a very challenging task. A more specific marker for stem cells in the heart is needed.

Additional Comments

- The existence of scar progenitor type fibroblasts in humans needs further confirmation. This could be a subtype of regular fibroblast.
- There are numerous risks inherent to this proposal, but the overall novelty of the idea makes the proposal very interesting.

Public Summary for DISC1-08792

Application #	DISC1-08792
Title (as written by the applicant)	Generation of bile duct-competent transplantable human liver organoids
Research Objective (as written by the applicant)	Generation of human stem cell-derived mini livers capable of exporting bile into the gallbladder after transplantation into the liver
Impact (as written by the applicant)	Mini livers capable of normal bile export would have potential for therapy of diseases in which bile export is impaired like Alagille syndrome.
Major Proposed Activities (as written by the applicant)	• Generation of mini livers using human stem cell-derived liver cells of different levels of maturity. • Identification of human stem cell-derived mini livers that are most effective in exporting bile into the gallbladder after transplantation into the livers of mice modeling Alagille syndrome. • Assessment and, if necessary, improvement of function, structure and growth of human stem cell-derived mini livers after transplantation into the livers of mice.
Statement of Benefit to California (as written by the applicant)	Many citizens of the state of California are in need for liver transplantation because of liver diseases associated with impaired bile flow. Because donor livers are sparse, many of these patients die while waiting for liver transplantation. Our research may generate a therapy that stabilizes liver function until a donor liver becomes available or may avoid the need for liver transplantation.
Funds Requested	$206,460
GWG Recommendation	***Tier 1 – Exceptional merit and warrants funding, if funds are available.***

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.

Median	90
Standard Deviation	2
Highest	95
Lowest	89
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	15
Tier 2 (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	3
Is the rationale sound?	11	0	4
Is the proposal well planned and designed?	11	0	4
Is the proposal feasible?	9	0	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 approach is exciting and is a high risk-high reward idea.
- The production of liver organoids with a biliary system would represent a significant advance. The proposed research would yield bile duct-competent human liver organoids that could be readily developed into a therapy for patients with Alagille syndrome.
- The proposed approach is well-motivated by development and disease.
- The *in vivo* evaluation is comprehensive and has a strong translational focus.

- There is high enthusiasm because of the prevalence of hepatic failure and the paucity of donor livers.
- Efficacy will be tested in two mouse models.
- The applicants are leaders in the field of stem cell based liver repair.

Concerns

- There is some concern about the ability of the organoid duct system to integrate with the liver biliary ducts.
- A complex multicellular approach will make the tissue better but also more complex, which will affect the anticipated goal of clinical translation.
- It is not clear whether the liver organoids will ultimately be functional with or without the bile duct. This is the high risk-high gain component of the application.

Additional Comments

- No relevant comments were made by the GWG.

Public Summary for DISC1-08796

Application #	DISC1-08796
Title (as written by the applicant)	In vivo screen for small molecules that regulate human hematopoietic stem cell engraftment and differentiation
Research Objective (as written by the applicant)	To identify small molecule treatments that enhance HSC engraftment or restrict their differentiation in order to develop disease-specific stem cell treatment
Impact (as written by the applicant)	The improved of efficacy of HSC transplantation therapy for patients with blood diseases by developing disease-specific transplantation protocols.
Major Proposed Activities (as written by the applicant)	• Aim 1. To screen for small molecules that alter human HSC behavior in an immune compromised xenograft mouse model. • Aim 1a. To screen for small molecules that alter human HSC differentiation. • Aim 1b. To screen for small molecules that alter human HSC engraftment. • Aim 2. To validate the small molecule candidates discovered in Aim 1.
Statement of Benefit to California (as written by the applicant)	CIRM has the ultimate goal of producing new stem cell therapies for the clinic. Our research has that specific goal in mind, as we will develop disease-specific HSC transplantation treatments that increase patient survival for a wide variety of hematological diseases. Our work has a high probability of improving health care for CA citizens, as we aim to improve a therapy that is already known to be safe in the clinic. We would be improving and expanding the types of therapies available.
Funds Requested	$222,480
GWG Recommendation	***Tier 2 – Not recommended for funding.***

Final Score: 66

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.

Median	70
Standard Deviation	10
Highest	84
Lowest	45
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (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	4	3
Is the rationale sound?	2	6	6
Is the proposal well planned and designed?	0	11	3
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

- Bringing an *in vivo* high-throughput screening technology to stem cell research is innovative and valuable.
- Aim 1(a) seems logical and will likely produce interesting results.

Concerns

- The proposed work is focused on screening small compounds in mouse hematopoietic stem cells (HSCs) using the Principal Investigator's strength in barcoding lineage outcomes. However, a number of issues make this proposal unfeasible including: the poorly-described human HSC validation, the possibility that compounds may not work

across different species, and a lack of description of the mouse model, which would likely not work for granulocyte outcomes.

- The experimental design seems a bit poor. There needs to be a comparison to existing screening (e.g., *in vitro*). The proposal also needs to propose the use of standard compounds in the field.
- Aim 1(b) is poorly developed and is not a trivial task.
- Aim 2 lacks appropriate detail.

Additional Comments

- Elements of this grant should definitely be re-crafted in new application(s), perhaps as a partnership with experts in specific aspects of biology or pharmacology.
- Reviewers considered if the mouse system could be tweaked to make it more applicable to human biology. There is some concern that the particular mouse model being used may not reflect a human environment for stem cell development.

Public Summary for DISC1-08798

Application #	DISC1-08798
Title (as written by the applicant)	The impact of regulatory T cells on neural precursor cell induced remyelination for the treatment of demyelinating diseases
Research Objective (as written by the applicant)	The scientific objective of the proposed studies is to determine how regulatory T cells impact the success of stem cell transplantation to treat demyelinating diseases.
Impact (as written by the applicant)	These studies may demonstrate an important role for regulatory T cells in promoting tissue regeneration and repair, and could assist with therapies for a number of different diseases.
Major Proposed Activities (as written by the applicant)	• We will first determine how a neural progenitor cell type derived from embryonic or induced pluripotent stem cells promote the generation and activity of regulatory T cells. • Next, we will determine if regulatory T cells are capable of activating endogenous regeneration and neurological repair pathways in the context of demyelinating mouse models. • We will determine if regulatory T cells augment the regenerative capacity of neural precursor cells under non-inflammatory conditions. • We will determine if blockade of DRAK2 signaling will enhance the outcome of NPC transplantation by enriching regulatory T cells near sites of demyelination.
Statement of Benefit to California (as written by the applicant)	The studies described in this application leverage important insight that resulted from work funded by the CIRM. The studies will be conducted in the State of California. Moreover, as California is home to a number of companies with an interest in stem cell transplantation, our studies could provide important information that could enhance the therapeutic potential of stem cell therapies. If successful, this could lead to additional employment opportunities in California.
Funds Requested	$202,680
GWG Recommendation	***Tier 2 – Not recommended for funding.***

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.

Median	65
Standard Deviation	0
Highest	65
Lowest	65
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (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?	6	7	1
Is the rationale sound?	1	10	3
Is the proposal well planned and designed?	0	9	5
Is the proposal feasible?	0	10	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 Principal Investigator (PI) is experienced.
- The proposal contains a very important problem to model.

Concerns

- The proposed work is highly complex, and it is not clear why a xenogeneic neural precursor cell (NPC) model is being tested in the context of Treg function and modulation of activity.
- The proposal has an extremely complex genetic model with multiple off-target effects (including those on the

immune system).

- There is poor justification for stem cell participation.

Additional Comments

- There was some indication as to how the findings will be moved forward, but no clear plan was stipulated. However, the testing and characterization of DRAK2 inhibitors poses a likely avenue for future research as would the optimization of iPSC patient-derived NPCs.

Public Summary for DISC1-08799

Application #	DISC1-08799
Title (as written by the applicant)	A Novel Method for Deriving Neuronal Progenitors for Parkinson's Disease Therapy
Research Objective (as written by the applicant)	The objective of this research is to provide a preferable approach to generate the autologous neural progenitors for the treatment of neurodegenerative disorders, such as Parkinson disease.
Impact (as written by the applicant)	The study will overcome several obstacles in regenerative therapies including the allogeneic rejections and tumor formation which may lay the foundation for stem cell therapy for Parkinson disease
Major Proposed Activities (as written by the applicant)	• Generation of neurospheres from iPSCs with ROCK inhibitor, EGF, heparin and under 10% CO2 culture conditions. • Infusion of neural progenitors into mouse brain and evaluation the efficiency of neuronal differentiation. • Evaluation of whether the neural progenitors will reverse the behavioral and neurochemical changes in Parkinson disease mouse model.
Statement of Benefit to California (as written by the applicant)	Parkinson's disease (PD) affects 2% of the elderly population in Califonia and worldwide. Medications is not an effective way of treatment due to the progressive death of dopaminergic neurons. The research will examine a novel approach to produce the neural progenitors to overcome several obstacles in regenerative therapies, including the allogeneic rejections and tumor formation. It would represent a significant advance in the development of stem cell therapy for neurodegenerative disorders.
Funds Requested	$250,240
GWG Recommendation	***Tier 2 – Not recommended for funding.***

Final Score: Below 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.

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

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (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?	2	7	6
Is the rationale sound?	0	8	7
Is the proposal well planned and designed?	0	11	4
Is the proposal feasible?	1	10	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 initial idea of breaking up the neurospheres to increase overall differentiation efficiency is interesting.

Concerns

- The novelty of the proposal is limited to a few technical modifications of an existing protocol.
- There is no convincing hypothesis or preliminary data supporting that the proposal will deliver exciting new results and advances.

- No data are presented indicating that the ability to generate the desired neuronal populations has been improved in any significant manner.
- Although it is interesting that increasing the CO_2 content of the growth conditions does appear to alter differentiation, the suggestion that there is improvement along any particular desired lineage is not supported by any data.
- Insufficient data are provided to give confidence in the rationale of the proposed approach.
- The experimental sequence to go from an increased number of neurons to an increased number of specific neurons is not made clear.

Additional Comments

- The slight change in the protocol might lead to significant changes in the end product but this hypothesis is not tested.
- A side-by-side comparison of existing methods with the one described here would have helped to increase enthusiasm.

Public Summary for DISC1-08800

Application #	DISC1-08800
Title (as written by the applicant)	Blood Brain Barrier (BBB)-on-Chip: Development and validation of a novel iPS-based microfluidic model of the human BBB
Research Objective (as written by the applicant)	To develop and systematically characterize a novel model of the human BBB using a microfluidic device (chip) and cells derived from induced pluripotent stem cells (iPSCs).
Impact (as written by the applicant)	The success of the proposed research will provide a novel, highly attractive model for screening of molecules to treat neurological disorders and for personalized medicine in the future
Major Proposed Activities (as written by the applicant)	• To develop a personalized model of the BBB-on-Chip using iPSC-derived brain microvascular endothelial cells (BMECs) and iPSC-derived neurons and astrocytes. • To perform a detailed profiling of small molecules crossing (or not) the human BBB from circulating blood using Mass Spectrometry. • To conduct a secretome profiling of peptides and proteins that are transported across the BBB with/without iPSC-derived neurons and astrocytes.
Statement of Benefit to California (as written by the applicant)	The state of California and its citizens will benefit from this project in a financial level as conducting this project at Cedars-Sinai will provide more job opportunities. Moreover, Emulate Inc. is planning to open a branch in the wet cost. Our successful collaboration will strongly promote California as their destination. Moreover, the Californian citizens will benefit from the potential development of new therapies for neurological disorders made available by this novel model
Funds Requested	$241,992
GWG Recommendation	***Tier 1 – Exceptional merit and warrants funding, if funds are available.***

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.

Median	90
Standard Deviation	3
Highest	94
Lowest	85
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	14
Tier 2 (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?	10	0	4
Is the rationale sound?	10	0	4
Is the proposal well planned and designed?	9	0	5
Is the proposal feasible?	9	0	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.

Strength

- The proposal is highly novel and innovative.
- The cells are from patients with relevant disease phenotypes.
- This approach provides a great corporate platform and a discovery platform. The chip model is impressive.
- The preliminary data are outstanding and support the proposal’s feasibility and disease relevance. In particular, the data showing a disease-relevant difference in BBB function is very impressive.

- There is an excellent plan for assessing small molecule transport.
- Overall, the proposal is great. The Principal Investigator deserves an enormous amount of credit for the proposal.

Concerns

- The sercretome analysis plan is simplistic in terms of the differentiation of neurons to astrocytes.
- The chip model has only half of the resistance of the actual BBB.

Additional Comments

- Portions of the application are sloppily put together. For example, the figures are messy and the table of contents is erroneous in certain parts.

Public Summary for DISC1-08813

Application #	DISC1-08813
Title (as written by the applicant)	IVD regeneration using iPSC-derived NP-progenitors in organ culture ex vivo system
Research Objective (as written by the applicant)	Our goal is to develop stem cell therapy for degenerated intervertebral disc using human induced pluripotent stem cells.
Impact (as written by the applicant)	This study aims to elucidate the potential of intervertebral disc (IVD) regeneration using induced pluripotent stem cells and to fulfill the unmet need for a cell source for IVD regeneration.
Major Proposed Activities (as written by the applicant)	• Assess survival and differentiation of human iPSC-derived NP progenitors in an IVD organ culture in induced early stage of degeneration and comparing to primary human NP cells. • Determine the potential of human iPSC-derived NP progenitors to repopulate a simulated degenerate IVD explant compared to porcine NP cells isolated from healthy and degenerate discs.
Statement of Benefit to California (as written by the applicant)	“My back hurts, Doc”. It’s one of the most common complaints heard by Californian family doctors. Traditional there is no good treatment today for disc degeneration. This study comes to promote future stem cell therapy for chronic back pain. Successful stem cell therapy will benefit all Californian residents by reducing workdays lose, medical costs and improving quality of life.
Funds Requested	$236,484
GWG Recommendation	***Tier 2 – Not recommended for funding.***

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.

Median	85
Standard Deviation	3
Highest	88
Lowest	75
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	12
Tier 2 (1-84): Not recommended for funding	3

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?	8	1	6
Is the proposal well planned and designed?	2	4	9
Is the proposal feasible?	7	2	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

- Vertebral disk repair using cell therapies would constitute a major advance.
- The project is significant and aims to advance our understanding of the potential of human induced pluripotent stem cell (iPSC)-derived nucleus pulposus (NP) progenitors to differentiate into functional NP cells suitable for IVD regeneration.
- The goal of the proposal is to generate a pool of NP cells that have been derived from iPSCs. If successful, these cells would serve a huge need in the field of disc repair. Creation of a NP-like population of cells and/or cells that could act like NP cells when placed in the disc would be a big leap forward in the field, assuming these cells could heal/halt damage to this structure.

Concerns

- Unfortunately, appropriate *in vivo* animal studies are not proposed. These would have provided a much better understanding of the therapeutic potential of iPSC-derived NPs for treatment of IVD degeneration.
- It is unclear if the cells used by the Principal Investigator are a true NP progenitor population.
- There are no safety studies planned on the purity of the NP progenitors and whether any selection or cell sorting will be required before transplantation. How well characterized are the cells?

Additional Comments

- The proposal would be improved by combining Aims 1 and 2 into a single Aim and creating a new Aim that better characterizes the fate of the stem cells (for example, through an array analysis or some other technique that would provide information on the type of cells that have been injected).
- Why are iPSCs proposed and not just allogeneic embryonic stem cells?
- The idea does not seem to be in the spirit of the Inception Program.

Public Summary for DISC1-08819

Application #	DISC1-08819
Title (as written by the applicant)	Organoid Modeling of Human Cortical Microcircuits
Research Objective (as written by the applicant)	The proposed studies will develop three-dimensional cell culture methods for creating human brain neural circuits for disease research and drug discovery.
Impact (as written by the applicant)	The proposed research will develop a new research platform for studying how neurons in the human brain function, how neurological disease subverts this activity, and how we might find new therapies.
Major Proposed Activities (as written by the applicant)	• Develop robust and reliable methods for creating three-dimensional organoid ("mini-brain") structures from human pluripotent stem cells. • Measure the ability of neurons within mini-brain structures to form functional connections with one another that resemble those seen in the human brain. • Determine how mini-brain neurons are organized at a larger network level to better model the normal and pathological activities of the human brain.
Statement of Benefit to California (as written by the applicant)	Neurological diseases are among the most debilitating medical conditions that affect millions of Californians each year, and many more worldwide. Few effective treatments for these diseases currently exist, in part because we know very little about the mechanisms underlying these conditions. Our proposed studies will develop an innovative cell culture platform to create a facsimile of human brain circuits that will enable us to better understand disease pathologies and discover new therapies.
Funds Requested	$230,400
GWG Recommendation	***Tier 1 - Exceptional merit and warrants funding, if funds are available***

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.

Median	90
Standard Deviation	6
Highest	97
Lowest	70
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	14
Tier 2 (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?	13	0	2
Is the rationale sound?	10	0	5
Is the proposal well planned and designed?	11	0	4
Is the proposal feasible?	10	1	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

- Successful development of three-dimensional cortical structures that contain excitatory and inhibitory neurons *in vitro* are a necessary step to model complex psychiatric diseases in a dish.
- The rigorous approach to the problem of organoid composition, which is critical to any disease-in-a-dish approach to understanding and therapy, is a key strength.
- The proposal is highly innovative and would establish a new product that could be used for drug screening approaches or for basic development questions regarding neuron networks.

- The use of lineage tracing and electrophysiological recording methods to establish cortical column formation and interconnectivity is a sophisticated approach for the establishment of "mini-brains".
- The preliminary data that show induction of cortical organoids from human induced pluripotent stem cells are quite impressive.
- The team is highly qualified to to conduct the proposed experiments.

Concerns

- In many psychiatric diseases, that diagnosis occurs after the disease onset. It would thus be imperative to compare any organoid structure from a diseased brain to a "normal brain". As each brain, diseased or normal, is inherently different for each person, it will be difficult to define the healthy baseline behavior of an organoid. This challenge should have been addressed.
- The degree to which the organoid parallels *in vivo* connectivity was questioned.
- Potential issues with using limited retroviral diversity to define clonality were expressed.

Additional Comments

- The proposal describes a very complicated problem and is crafted beautifully and carefully. Care should be administered so as not to lose sight of the ultimate goal.
- The Applicant stresses the aspect of reproducibility which is a positive factor.

Public Summary for DISC1-08823

Application #	DISC1-08823
Title (as written by the applicant)	Novel Platforms to Enhance In Vivo Delivery of Skeletal Muscle Progenitor Cells from Human Pluripotent Stem Cells
Research Objective (as written by the applicant)	Delivery of muscle stem cells presents a major roadblock for therapy. We explore novel approaches to increase the efficiency of delivering and monitoring muscle stem cells derived from hPSCs.
Impact (as written by the applicant)	Development of enhanced monitoring and delivery platforms will greatly accelerate translational strategies aimed at delivering muscle stem cells for transplantation to patients with muscle disease.
Major Proposed Activities (as written by the applicant)	• Aim 1. Develop a mesoporous silica nanoparticle (MSNP) platform to deliver controlled and localized release of small molecules to enhance SMPCs engraftment *in vivo*. • Aim 2. To develop a high throughput system using a multiplexed bioluminescence imaging (BLI) platform to enable evaluation of SMPC survival and engraftment *in vivo*.
Statement of Benefit to California (as written by the applicant)	Skeletal muscle wasting disorders including muscular dystrophies, atrophy or aging will affect subsets if not all California (CA) residents during his/her lifetime. Replacement of exhausted muscle stem cells with new stem cells could provide a renewable source of muscle stem cells to extend life span and/or enhance quality of life of citizens of CA. Improved health of CA citizens will also reduce the health care costs associated with muscle disease that occur over the lifetime of CA residents.
Funds Requested	$230,400
GWG Recommendation	***Tier 1 - Exceptional merit and warrants funding, if funds are available.***

Final Score: 88

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.

Median	87
Standard Deviation	3
Highest	95
Lowest	85
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	15
Tier 2 (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	1	2
Is the rationale sound?	10	0	5
Is the proposal well planned and designed?	9	2	4
Is the proposal feasible?	9	0	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

- This is a well designed proposal based on convincing preliminary data. The aims can be addressed in the proposed time frame with the requested support.
- The risks are suitably addressed. For example, the pH dependent release of small molecules from nanoparticles must be tested experimentally.

Concerns

- No significant concerns were expressed by the GWG.

Additional Comments

- It would be ideal to develop the bioluminescence imaging (BLI) platform to have a minimally invasive way to quantify fusion.
- The application contains a reasonable timeline for the proposed budget.

Public Summary for DISC1-08825

Application #	DISC1-08825
Title (as written by the applicant)	Reverse transcriptase inhibitors as a novel therapeutic approach for neurological autoimmune disorders
Research Objective (as written by the applicant)	We found that approved anti-retroviral drugs could stop inflammation and block neurodegeneration. We propose to validate the re-purpose efficacy of these clinically-approved retroviral drugs.
Impact (as written by the applicant)	We have identified an unexpected cause to a brain inflammation and a potential simple treatment. Our research could help millions of patients affected by a broad range neuro-immunological disorders.
Major Proposed Activities (as written by the applicant)	• Determine the specificity of the anti-retroviral drugs to inhibit cellular reverse transcriptase and reduce human neurodegeneration. • Determine the molecular mechanism responsible for the observed neuronal toxicity. • Determine the non-cell autonomous component of neuro-inflammation using co-culture cellular assays.
Statement of Benefit to California (as written by the applicant)	Neuroinflammation is an important component of several neurological disorders, including autism, ALS, Parkinson, Alzheimer, lupus, multiple sclerosis and aging. These conditions affects millions of people in California and worldwide. However, little is known about what initiates such an inflammatory process. Our innovative approach is of high clinical relevance, because it suggests that patients suffering with neuroinflammation could immediately benefit from available anti-retroviral drugs.
Funds Requested	$232,200
GWG Recommendation	***Tier 1- Exceptional merit and warrants funding, if funds are available.***

Final Score: 98

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.

Median	99
Standard Deviation	2
Highest	100
Lowest	95
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	15
Tier 2 (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

- The research is extremely novel, very relevant to the CIRM mission and based on beautiful science.
- The research offers a clear path to treatment for devastating diseases that are currently untreatable.
- The proposed work is extremely exciting and beautifully conceived with clear and relevant clinical translation. The therapeutic agents needed to move to the clinic are already approved for other purposes, thus enabling efficient movement to clinical trials.

- This is an exciting and beautifully rationalized application with a very high impact and a clear path to the clinic. Outstanding!

- Exceptionally relevant grant with outstanding ideas and a clear clinical direction going forward with novel approaches as well. What is not to like?

Concerns

- No significant concerns were expressed by the GWG.

Additional Comments

- Aim 2 is critical to establish the mechanism.

Public Summary for DISC1-08828

Application #	DISC1-08828
Title (as written by the applicant)	Genomic analyses of single human hepatocyte stem cells
Research Objective (as written by the applicant)	The purpose of the proposal is to identify human hepatocyte stem cells through genomic characterization of single cells. Such stem cells have recently been revealed in mouse, but not yet in humans.
Impact (as written by the applicant)	Successful completion of this proposal will reveal subsets of human hepatocytes and indicate the presence of hepatocyte stem cells - cells with enormous therapeutic potential to treat cirrhosis.
Major Proposed Activities (as written by the applicant)	• Single cell seq analysis of human hepatocytes. • Staining of human liver for markers identified in single cell seq. • Characterization of genome accessibility of single hepatocyte cells.
Statement of Benefit to California (as written by the applicant)	Cirrhosis is a severe condition with liver transplant representing the only definitive treatment. Insufficient supply of livers limits the ability to treat most patients in California with liver cirrhosis. Identification of hepatocyte stem cells in human liver would then provide the basis for isolating these cells and using them as a cell-based therapeutic. This new approach has strong potential to bring cellular therapies to a much larger number of Californians with cirrhosis.
Funds Requested	$237,564
GWG Recommendation	***Tier 2 - Not recommended for funding.***

Final Score: 81

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.

Median	80
Standard Deviation	8
Highest	95
Lowest	60
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	5
Tier 2 (1-84): Not recommended for funding	10

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	1	6
Is the proposal well planned and designed?	4	7	4
Is the proposal feasible?	5	4	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 identification, isolation, and culturing of the human hepatocyte stem cells (by single-cell RNA-seq) and subsequent use as a therapeutic to treat liver cirrhosis are a primary strength.
- The proposed study will provide insights into the heterogeneity of hepatocytes. It is important to survey the single-cell transcriptomics of liver stem cells, so a proposal such as this is high priority.
- This is an interesting approach (though possibly underpowered). It will provide important insight for follow-up on liver (stem) cell biology/heterogeneity. This application fits well in my view into the “great idea” concept of the Discovery Inception Program.

Concerns

- This is an underpowered study - 3 humans, 100 cells each. This is probably in response to the constraints of limited funding. However, this weakness could be more clearly addressed, and a strategy to obviate this problem proposed. For example, could the investigators prescreen human liver cells for those that are high and low in TERT expression? Then they could sequence more of these TERT high cells and determine the variance of this population for later functional studies.

- The normal liver tissue is not from normal liver (admittedly obtaining normally healthy liver is problematic) but are obtained from "normal tissue from liver resections from liver cancer patients and liver biopsies obtained from patients during pancreatectomy for pancreatic cancer". For example, exosomes released from distant cancer cells influence macrophage will prepare a metastatic niche in the liver, and therefore, such liver biopsies should not be construed as "normal liver tissue."

- There is a lack of power estimation, which hurts the competitiveness of the proposal.

- A number of reviewers thought a more focused study of TERT positive cells would be more powered, so this should have been discussed as an alternative.

- A more explicit discussion of constraints would have enabled a better sense of whether more cells could have been assayed to increase power (i.e., what does each experiment cost)?

Additional Comments

- A power analysis might help.

Public Summary for DISC1-08834

Application #	DISC1-08834
Title (as written by the applicant)	Developing new methods to monitor ES and iPS cell-derived human hepatocyte homing and engraftment in vivo
Research Objective (as written by the applicant)	To develop new methods for imaging hepatocytes (derived from ES and iPS cells) after they are injected into patients.
Impact (as written by the applicant)	This work could provide a new method to enable the direct quantification and visualization of key steps in the successful use of hepatocytes to treat liver disease.
Major Proposed Activities (as written by the applicant)	• Determine the best conditions for loading hepatocytes with the PET imaging probes [18F]-DFA, [18F]-2-DFR, and [18F]-FDG. • Inject the pre-loaded hepatocytes into mice and image them as they traffic through circulation, home, and engraft at different sites in the body.
Statement of Benefit to California (as written by the applicant)	Liver failure is a leading cause of death among Californians. Cell-based therapies to regenerate the liver hold great promise for treating liver failure. Getting these cell-based therapies to the clinic however will require the development of new tools to monitor their behavior once inside the patients. The proposed research develops one such tool. If successful, this approach could provide a method for watching as hepatocytes, injected into patients, home and engraft in the liver.
Funds Requested	$230,400
GWG Recommendation	***Tier 2 – Not recommended for funding.***

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.

Median	75
Standard Deviation	9
Highest	85
Lowest	60
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	3
Tier 2 (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?	6	3	6
Is the rationale sound?	3	3	9
Is the proposal well planned and designed?	4	5	6
Is the proposal feasible?	3	3	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

- There is a clear need for a reliable marker and imaging technology to trace cell implants.
- Making use of a hepatocyte specific metabolic pathway for cell specific probe retention is attractive.
- An important innovation is to develop PET imagining probes that can be retained in hepatocytes.
- Addresses an important need by trying to better understand homing and engraftment of *in vitro* derived hepatocytes

Concerns

- Determine whether the pre-loaded embryonic stem cell and induced pluripotent stem cell-derived human cells (hepatocytes) can be imaged as they home and engraft throughout the body. The probe has not been suitably tested in human iPSC derived hepatocytes.
- It is not clear if the mouse findings (both the results and the imaging) would work equally in human.

Additional Comments

- The route of administration (intra-splenic) appears irrelevant for a clinical application.
- Perhaps transplanting liver stem cells, rather than differentiated hepatocytes, would allow cells to find niches, persist, expand, differentiate, and assume long term liver function.

Public Summary for DISC1-08842

Application #	DISC1-08842
Title (as written by the applicant)	Identification of stem cell surface markers as potential therapeutic targets for advanced prostate cancer
Research Objective (as written by the applicant)	The goal of this proposal is to identify proteins found on the surface of both human prostate stem cells and cancer cells that could be used as potential targets for treating advanced prostate cancer.
Impact (as written by the applicant)	There is no cure for advanced prostate cancer. This combined with the success of treating other cancers by targeting features unique to stem cells highlight the potential impact of our proposal.
Major Proposed Activities (as written by the applicant)	• Characterize human prostate stem cell subpopulations found in normal tissue by their molecular signatures and functional traits. • Identify unique markers found on the surface of prostate stem cells that are also overexpressed in advanced prostate cancers. • Develop antibodies against prostate stem cell associated surface markers and test their ability to target advanced prostate cancer.
Statement of Benefit to California (as written by the applicant)	Prostate cancer accounts for approximately 3,500 deaths each year in California. The lack of effective treatments for advanced prostate cancer and the appearance of resistance mechanisms to current drugs underscore the need to develop new therapeutic strategies. Our approach of targeting normal stem cell traits that are also found in advanced prostate cancer could potentially revolutionize how we treat men living with this debilitating disease.
Funds Requested	$230,400
GWG Recommendation	***Tier 1 – Exceptional merit and warrants funding, if funds available.***

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.

Median	90
Standard Deviation	1
Highest	92
Lowest	85
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	14
Tier 2 (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	2
Is the rationale sound?	11	0	3
Is the proposal well planned and designed?	10	0	4
Is the proposal feasible?	5	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

- A novel finding to be explored is whether advanced prostate cancer overexpresses normal stem cell surface markers. Studying normal tissue stem cells may provide novel targets and strategies for treating currently fatal cancers.
- Aims logically progress to characterize antibody in animal models of prostate cancer and determine off-target toxicities in a mouse model that expresses the human ortholog.
- The Principal Investigator has experience taking antibodies to the clinic by leveraging companies.
- Single-cell analysis of tumors is a very important area of research, including understanding how subpopulations are related to each other and the how subpopulations transition from one to another.

- The approach offers a tractable way to achieve *ex vivo* gene therapy to effect positive outcomes for Hemophilia A.
- This project has excellent medical significance with clear and obvious translational prospects.
- Even partial engraftment would be expected to have positive clinical outcomes.
- The preliminary data is strong.

Concerns

- The grant seems overambitious for the amount of funds supplied and a 1-year time frame. Perhaps just Aim 1 would have been appropriate scope.
- I am not sure that normal cells (particularly at a single cell level) taken from a patient with prostate cancer and histologically separated are truly normal.
- I am not sure that markers that vary between stem-cell populations are inherently good therapeutic targets. One might also suppose that markers that do NOT vary between these populations might also be good targets. Or how about a marker expressed ONLY (or specifically) in a particular subpopulation that shows particular characteristics of aggressiveness.
- There are some concerns about how long engrafted sinusoidal endothelial cells will persist upon transplantation.

Additional Comments

- No relevant comments were made by the GWG.

Public Summary for DISC1-08845

Application #	DISC1-08845
Title (as written by the applicant)	Sending foes against foes – Using genetically modified cancer stem cells to fight cancer stem cells.
Research Objective (as written by the applicant)	To use genetically-modified cancer stem cells (eventually derived from a patient's tumor) to seek out cancer in metastatic and dormant niches and, by enhancing local immunity, to eliminate them.
Impact (as written by the applicant)	By concurrent elimination of both CSCs and bulk tumor cells by the modified CSCs, one would predict this kind of personalized, non-toxic therapy to effect a cure.
Major Proposed Activities (as written by the applicant)	• Establish the non-growing, immune cell-attracting, and inducibly-suicidal CSCs and test the potential to change the characteristics of the tumor stem cells. • Determine T cell recruitment, immune clearance in both primary and metastatic sites by administration of the genetically modified CSCs *in vivo*.
Statement of Benefit to California (as written by the applicant)	Cancer is the second leading cause of death in the population of California. Development of non-toxic therapies with the potential to be curative would have enormous social impact. New therapeutic approaches are expensive initially, but if successful, the proposed treatment could become very economical since it would replace what are sometimes multiple rounds of different and often very expensive therapies, and would reduce morbidity and mortality and the economic impact of lost productivity.
Funds Requested	$180,000
GWG Recommendation	***Tier 2 - Not recommended for funding***

Final Score: Below 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.

Median	---
Standard Deviation	---
Highest	---
Lowest	---
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (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?	6	4	4
Is the rationale sound?	1	9	4
Is the proposal well planned and designed?	0	11	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

- The team is strong.

Concerns

- This is a very overly ambitious proposal which has many challenges and limited feasibility.
- There is insufficient consideration of cellular homing.
- Good medical impact, if successful, exists but has many problems.

- The vision for future human clinical impediments is not well considered.
- Immortalized cancer cell lines may not model tumors well since they are sort of a tumor on the basis of being immortalized.

Additional Comments

- No relevant comments were expressed by the GWG.

Public Summary for DISC1-08848

Application #	DISC1-08848
Title (as written by the applicant)	Embryonic Stem Cells for Corneal Endothelial Degeneration
Research Objective (as written by the applicant)	The proposed studies will determine the optimal approaches to differentiate and transplant stem cell-derived corneal endothelial cells.
Impact (as written by the applicant)	These data will provide foundational proof-of-concept data that will allow the rapid advance of a cell therapy towards clinical application.
Major Proposed Activities (as written by the applicant)	• Determine optimal conditions to generate human corneal endothelial cells from human stem cells, assaying both cellular and functional markers. • Test efficacy in a rabbit model that closely mimics human injury or degeneration, examining disease-relevant functional assays.
Statement of Benefit to California (as written by the applicant)	1. Employing California's citizens in the research funded through CIRM and thereafter as this project advances. 2. Developing a first-in-class treatment for California's citizens with corneal diseases affecting their vision.
Funds Requested	$237,564
GWG Recommendation	***Tier 1 - Exceptional merit and warrants funding, if funds are available***

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.

Median	90
Standard Deviation	1
Highest	92
Lowest	90
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	14
Tier 2 (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?	11	0	3
Is the rationale sound?	11	0	3
Is the proposal well planned and designed?	11	0	3
Is the proposal feasible?	11	0	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 rationale is convincing that there is an unmet need to develop ESC-derived human corneal endothelial cells for the treatment of corneal endothelial cell dysfunction.
- The proposed method to improve differentiation to corneal endothelial cells is innovative.
- The proposal contains excellent structural and functional characterization of the cells *in vitro* and *in vivo*.
- The *in vivo* model is appropriate.

- There is a clear path to translation.
- The Principal Investigator is well-positioned to conduct this project.

Concerns

- No significant concerns were expressed by the GWG.

Additional Comments

- Both *in vitro* differentiation and *in vivo* experiments in the preclinical model are critical.

Public Summary for DISC1-08855

Application #	DISC1-08855
Title (as written by the applicant)	Modulating Liver Sinusoidal Endothelial Cell Permeability to Enhance Engraftment of Endothelial Cell Progenitors for the Treatment of Hemophilia A
Research Objective (as written by the applicant)	We aim to demonstrate that regulators of endothelial cell permeability can foster engraftment of endothelial cell progenitors in the liver sinusoids leading to production of Factor VIII.
Impact (as written by the applicant)	Our work would provide conceptual proof that a cell based therapy for hemophilia A is possible and should be pursued.
Major Proposed Activities (as written by the applicant)	• Demonstrate that endogenous production of cytokine in mice with liver injury is responsible for the high engraftment of donor endothelial cells. • Demonstrate that liver endothelial cells respond to regulators of endothelial cell permeability in the same manner as other types of endothelial cells. • Demonstrate that administration of regulators of endothelial cell permeability can enhance the engraftment of human endothelial cells in the livers of immunodeficient mice. • Demonstrate that endothelial progenitors generated from human induced pluripotent stem cells can engraft the livers of mice, produce Factor VIII and alleviate the symptoms of hemophilia A.
Statement of Benefit to California (as written by the applicant)	Hemophilia A is a life-threatening disease that affects about 1 in 5000 male births. Life-long therapy is required to help patients with this disease and this therapy suffers from complications from inhibitor production that can limit its benefits. Development of a cell therapy to treat hemophilia A may provide a long-lasting therapy or even cure for the disease greatly impacting the lives of the patients and the economic burden that the disease places on the patients and the medical system.
Funds Requested	$180,000
GWG Recommendation	***Tier 1 – Exceptional merit and warrants funding, if funds are available.***

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.

Median	90
Standard Deviation	0
Highest	90
Lowest	90
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	14
Tier 2 (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	1	1
Is the rationale sound?	9	1	4
Is the proposal well planned and designed?	9	1	4
Is the proposal feasible?	7	1	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

- Even a modest level of normal FVIII production (1-10%) could dramatically improve the health of hemophilia A patients.
- The overall goal of the proposal contains excellent translatability and medical significance.
- The proposal has strong preliminary data to show that LSECs can be made from human pluripotent cells and good engraftment in mouse model.

Concerns

- Thrombin may be too harsh of a treatment for the patient to tolerate.
- There is some concern about the long term survival of engrafted cells.

Additional Comments

- Future directions are to improve the efficiency of generating patient-specific pluripotent stem cells and develop methods of gene-editing to insert a Factor VIII cDNA in to restore normal Factor VIII production.

Public Summary for DISC1-08856

Application #	DISC1-08856
Title (as written by the applicant)	Cardiac disease modeling in pig hearts using human ARVD patient-specific induced pluripotent stem cell-derived cardiomyocytes
Research Objective (as written by the applicant)	To build better and more clinically relevant human heart disease models using large animal hearts and patient-specific stem cell derived heart cells.
Impact (as written by the applicant)	If we can establish better human disease models using large animal hearts and heart cells derived from human stem cells, these animals could be used for drug testing without involving human subjects.
Major Proposed Activities (as written by the applicant)	• Injecting heart cells derived from human stem cells to large animal hearts to determine the best method of keeping injected heart cells in the best health state. • Injecting diseased heart cells derived from human ARVD patients to large animal hearts to determine the best method of inducing disease state.
Statement of Benefit to California (as written by the applicant)	Heart conditions leading to death or bad heart functions in young adults often are the results of gene mutations inherited from parents. Recent progress in reprogramming skin cells to patient-specific stem cells enables modeling human disorders in cultures. We propose to establish live animal heart models of human heart diseases using patient-specific stem cell derived heart cells so as to develop new therapeutic strategies benefiting California young citizens who have inherited heart diseases.
Funds Requested	$229,310
GWG Recommendation	***Tier 2 – Not recommended for funding.***

Final Score: 72

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.

Median	70
Standard Deviation	4
Highest	80
Lowest	65
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (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?	8	4	3
Is the rationale sound?	1	5	9
Is the proposal well planned and designed?	0	8	7
Is the proposal feasible?	1	7	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 significance of the proposal is in *in vivo* modeling of human inherited cardiomyopathy in the large preclinical model hearts using differentiated patient induced pluripotent stem cells (iPSCs).
- A strength of the proposal is the advance in Arrhythmogenic Right Ventricular Dysplasia (ARVD) modeling, which has been challenging. A source of ARVD cells has strong potential to advance understanding of this disease.

Concerns

- It is unclear how the *in vivo* pig model will be better than already published by the Principal Investigator (PI) *in vitro* iPSC-cardiomyocyte (iPSC-CM) maturation approach. It appears provides a good model for ARVD pathology
- It is unclear how human ARVD-CM will be harvested and purified from the pigs' hearts and used for planned analyses by electron microscopy, immunohistochemistry, qPCR, western blots, Co-immunoprecipitation, mRNA expression microarrays, electrophysiological (EP) recordings and Seahorse metabolic flux analyzer. How will the cardiac myocytes be separated?
- The proposal needs a stronger argument for need of more complex preclinical model experiments since mouse data is promising.
- The PI presents compelling preliminary data indicating that iPSC-cardiomyocytes can be matured *in vitro* and in a rodent model, raising questions as to why transition to a much more complex preclinical model is necessary.
- There are significant feasibility concerns regarding obtaining sufficient numbers of viable cells after one month in the preclinical model, and in separating the human cells from pig cells.

Additional Comments

- What are the advantages of a preclinical model compared to *in vitro* maturation?
- It is not clear whether enough cells can be collected for analysis.
- Alternatives using directly CRISPR induced pig KO could be more informative and technologically less expensive.

Public Summary for DISC1-08868

Application #	DISC1-08868
Title (as written by the applicant)	Developing a personalized approach to beta cell replacement for patients with a genetic form of diabetes
Research Objective (as written by the applicant)	To correct a gene mutation in a patient's stem cells and produce functional replacement cells for the patient to cure their diabetes.
Impact (as written by the applicant)	We expect that this project can serve as a model for developing new treatments for patients with certain forms of genetic diabetes.
Major Proposed Activities (as written by the applicant)	• To understand how the patient's gene mutation affects the differentiation, function, and survival of stem cell derived insulin cells • To correct the patient's mutation in stem cells, then generate new insulin cells and test if they are fully functional.
Statement of Benefit to California (as written by the applicant)	California is already a leader in advancing stem cell technology. If we are successful, we believe that California can become the center for patients with certain forms of diabetes to come to for treatment.
Funds Requested	$180,000
GWG Recommendation	***Tier 1 – Exceptional merit and warrants funding, if funds are available.***

Final Score: 86

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.

Median	86
Standard Deviation	4
Highest	95
Lowest	80
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	11
Tier 2 (1-84): Not recommended for funding	3

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	3
Is the rationale sound?	10	0	4
Is the proposal well planned and designed?	7	1	6
Is the proposal feasible?	8	2	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

- This proposal presents a rare opportunity to cure diabetes. The proposal takes advantage of "an experiment of nature" to study a particular disease-causing mutation in EXACTLY the genetic milieu of the human with the disease.

- The significance of the proposal is in using induced pluripotent stem cells from a patient with a key homozygous null mutation to
    - study genome correction therapy.
    - learn about human pancreatic endocrine cell development and maintenance.
    - gain experience in islet regeneration to treat diabetes.

- If successful, the research could lead towards a gene therapy for the proband.
- The experiments should broadly inform the basic biology of Maturity Onset Diabetes of the Young (MODY) and other endocrine disorders.

Concerns

- More discussion should have been included as to why the following paper does not "scoop" the proposed work: *Diabetes*. 2015 Jul;64(7):2497-505. doi: 10.2337/db14-1412. Epub 2015 Feb 3. “The Basic Helix-Loop-Helix Transcription Factor NEUROG3 Is Required for Development of the Human Endocrine Pancreas.”
- Too few details are provided on pancreatic endocrine differentiation from human embryonic and induced pluripotent stem cells.

Additional Comments

- Future steps should involve partnering with translational researchers or a company to design a transplantation strategy as a personalized cellular therapy for patients in more clinically relevant diabetes models.

Public Summary for DISC1-08878

Application #	DISC1-08878
Title (as written by the applicant)	Functional characterization of pluripotency exit-associated enhancers
Research Objective (as written by the applicant)	Functional characterization of enhancers required to exit from pluripotency and achieve neural induction. In addition, development of differentiation techniques without the use of extrinsic factors.
Impact (as written by the applicant)	Creating an important catalog of functional enhancers that associate with pluripotency exit and neural induction. Improving technologies for stem cell maintenance, differentiation, and reprogramming.
Major Proposed Activities (as written by the applicant)	• Massively parallel characterization of pluripotency exit-associated enhancers. • Identification of pluripotency exit determining enhancers using high-throughput CRISPR/Cas9 activation.
Statement of Benefit to California (as written by the applicant)	Stem cells maintenance and differentiation is dependent upon dynamic gene regulatory changes. While few datasets exist that have characterized these regulatory changes, the techniques used are descriptive. Here, we plan to functionally characterize thousands of these sequences for their regulatory activity. In addition, we plan to use the elements we characterize to drive differentiation without the use of extrinsic factors, thus providing novel and safer methods for stem cell differentiation.
Funds Requested	$209,000
GWG Recommendation	***Tier 2 – Not recommended for funding.***

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.

Median	85
Standard Deviation	9
Highest	99
Lowest	65
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	9
Tier 2 (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?	10	2	3
Is the rationale sound?	12	2	1
Is the proposal well planned and designed?	9	3	3
Is the proposal feasible?	10	1	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

- Understanding of enhancer function could really impact many CIRM projects and accelerate all of them.
- There is strong preliminary data.
- The Principal Investigator's (PI) track record is excellent.
- There is a great return for the investment.
- This is a clear and interesting basic biology proposal.

Concerns

- It is clear that the experiments will generate a large pool of very useful data regarding enhancer function in stem cells, but there is no “product” that will be produced.
- The proposal is limited by the lack of caveats, translational vision (enhancer activation) – the unrealistic, short differentiation timeline limits the types of enhancers included.
- There is some concern that the approach is highly basic in nature (though interesting) and the proposed research lacks the translatability and vision for moving beyond basic science.

Additional Comments

- The PI mentioned very briefly the possibility of using the CrispR/Cas9 system to potentially differentiate cells by activating enhancers. This is a really neat idea, but is not discussed in detail.

Public Summary for DISC1-08882

Application #	DISC1-08882
Title (as written by the applicant)	Matching Cell Grafts to Patients: A Tissue-Engineering Approach to Select iPSC-derived Cardiac Myocytes for the Individual Patient
Research Objective (as written by the applicant)	The main goal of this project is to develop the proof-of-concept benchmarks for a novel in vitro assay that will help physicians select a cellular transplant for patients with heart failure
Impact (as written by the applicant)	This testing will accelerate and individualize the process of pairing patients with cell transplants
Major Proposed Activities (as written by the applicant)	• To improve our culture conditions to grow human cardiac myocytes in the laboratory for testing. • To develop our biomaterial methods on humans that can test the interaction of muscle cells to its environment in the native heart. • To test the ability of this technology and begin build a clinical test to support the physician's choice for a cardiac cell graft.
Statement of Benefit to California (as written by the applicant)	In 2009, 259 Californians died per 100,000 due to heart disease despite access medical care. Cell-based therapies may help alleviate this problem if they can improve a patient's heart function. Our group has developed a method to derived biomaterials that could dramatically help physicians to choose a compatible cell graft likely to survive in a patient's own heart. We aim to test the ability of this technology and build a clinical test to support the physician's choice for a cardiac cell graft.
Funds Requested	$235,800
GWG Recommendation	***Tier 2 – Not recommended for funding.***

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.

Median	75
Standard Deviation	12
Highest	84
Lowest	50
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (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?	6	4	5
Is the rationale sound?	2	7	6
Is the proposal well planned and designed?	1	8	6
Is the proposal feasible?	0	8	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 idea of age of the extracellular matrix (ECM) influencing the outcome of the experiments is novel. A better understanding of iPSC-cardiomyocyte interactions with the ECM is necessary to obtain effective engraftment *in vitro*.
- The preliminary data is compelling.
- There is a strong translational component.

Concerns

- There are concerns that engraftment *in vitro* may not represent *in vivo* functionality. Thus, feasibility is a concern.
- The proposal lacks a functional assessment of cells. Adequate details regarding the cell types to be integrated are not provided.
- The path to translation is difficult to follow. It seems unlikely that autologous ECM from a heart failure patient would be used in a treatment.
- It is not clear what cells are used.
- The ECM is not well characterized.

Additional Comments

- No relevant comments were expressed by the GWG.

Public Summary for DISC1-08886

Application #	DISC1-08886
Title (as written by the applicant)	Single Cell Deconvolution of Mesodermal Priming from the Human Pluripotent State
Research Objective (as written by the applicant)	Using new single cell analysis tools, identify the 'mesodermal primed state' in human pluripotent stem cell culture from which specialized blood and muscle cell types can most efficiently be made.
Impact (as written by the applicant)	If this state can be identified and generally induced in hPSCs it would represent a new and efficient mechanism to catalyze the productions of future blood and muscle regenerative material.
Major Proposed Activities (as written by the applicant)	• Create a comparative molecular and proteomic single cell profile of hPSC lines displaying different mesodermal potency. • Induce a mesodermal 'primed' state in hPSCs in undifferentiated culture conditions using optimized inducible gene transduction methods.
Statement of Benefit to California (as written by the applicant)	The production of transplantable mesodermal (i.e. blood and muscle) cell products from human pluripotent cells (hPSCs) remains elusive. It is also becoming clear that not all human pluripotent cell lines and culture systems are the same. We believe that a state where human cells are 'primed' to become mesoderm exists and is stable. our study aims to identify this state, prove it can be induced, and thus act as a catalyst for generating these regenerative products in the future.
Funds Requested	$237,564
GWG Recommendation	***Tier 2 – Not recommended for funding.***

Final Score: 57

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.

Median	---
Standard Deviation	---
Highest	---
Lowest	---
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (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?	1	8	5
Is the rationale sound?	0	8	6
Is the proposal well planned and designed?	1	7	6
Is the proposal feasible?	2	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

- The proposal contains excellent single cell proteomics; the applicant is a leader in the field.

Concerns

- The significance of project is limited and expected results are unlikely to accelerate or increase our understanding of the basic biology or clinical translation of human stem cells.

- The proposed work is focused on optimizing proteomic analysis of two different, albeit genetically identical hiPSC lines, which show some difference in mesoderm lineage outcomes. The focus is very narrow and not well justified, and seems more like a technological approach in search of a biological read out.
- There is no clear rationale for choosing the two iPSC lines.
- The proposal lacks critical controls – gold standard human ESCs or other iPSCs.
- There is insufficient justification for Aim 2 and mir155 experiments.

Additional Comments

- The translational value is questionable. Differences in differentiation may be due to culture conditions, passage etc. The most likely clinical scenario is that cell lines will be chosen based on their susceptibility for directed differentiation.
- Genetic manipulation will very likely not be applied or necessary to improve differentiation towards a certain fate.

Public Summary for DISC1-08891

Application #	DISC1-08891
Title (as written by the applicant)	Novel chondroprotective agonists of gp130 signaling
Research Objective (as written by the applicant)	The proposed work is designed to optimize a gp130 agonist for future therapeutic development, verify its molecular mechanism and test its function in rat models of osteoarthritis and cartilage repair
Impact (as written by the applicant)	Successful advancement of a novel gp130 agonist toward therapeutic development could generate a new treatment paradigm for slowing osteoarthritis progression or possibly event prevent its development
Major Proposed Activities (as written by the applicant)	• Scale up production of a novel gp130 agonist and its chemical derivatives. • Evaluate the drug-like qualities and the signaling induced by these new derivatives in direct comparison to the parent molecule; choose the best candidate. • Verify that the parent agonist and the best derivative function as agents that induce gp130 homodimerization in the absence of ligand. • Conduct six week studies of the best derivative in a rat focal cartilage defect model and a degenerative rat medial meniscal tear (MMT) model. • Histologically score proliferation, apoptosis, matrix character, ossification, catabolic enzyme levels and establish OARSI scores In both models. • Perform RNA-seq on chondrocytes to compare treated vs. sham controls in both models.
Statement of Benefit to California (as written by the applicant)	Hundreds of thousands of Californians suffer osteoarthritis (OA). Proposed work is designed to advance development of a new medicine for OA treatment and/or prevention. Currently, the medicines used to treat OA are mostly for pain management and do not slow the progression of the disease. If these experiments are successful, they will reveal a new line of thought in the treatment of OA and may eventually directly lead to a therapy that targets the cause of OA rather than the symptoms.
Funds Requested	$250,200
GWG Recommendation	***Tier 2 - Not recommended for funding.***

Final Score: 81

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.

Median	80
Standard Deviation	3
Highest	85
Lowest	75
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	4
Tier 2 (1-84): Not recommended for funding	11

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	4
Is the rationale sound?	7	3	5
Is the proposal well planned and designed?	0	3	12
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

- The application describes developmental stage pharmaceuticals that can affect chondrogenesis, a much needed medical advance.
- Some mechanistic insights into signaling pathways may be forthcoming.

Concerns

- This is not a stem cell application (the word stem cells is not even mentioned anywhere in the proposal). No discussion of a stem cell population and/or development of a stem cell product is provided.

- The Principal Investigator notes, just prior to the aims, that if the proposal is successful, a large preclinical model will be used. No details are provided on how, or what model will be used.
- The proposal contains a hypothesis that is not a stem cell question.
- It would be an Improved proposal if it was written from the point of view of stem cells.
- There are some concerns about identifying which cells are specifically targeted.

Additional Comments

- No relevant comments were expressed by the GWG.

Public Summary for DISC1-08899

Application #	DISC1-08899
Title (as written by the applicant)	Cell therapy for Type 1 Diabetes using a novel thin-film encapsulation device with human insulin-producing beta cell-like clusters derived from pluripotent cells.
Research Objective (as written by the applicant)	Our goal is final validation of our cell encapsulation device in a large animal (swine) to simulate human engraftment. Protection, viability and function of beta cell-like clusters will be assessed.
Impact (as written by the applicant)	Bringing this novel cell encapsulation device to clinical readiness will allow safe cell replacement therapy with unprecedented patient comfort in a long term cure to diabetes.
Major Proposed Activities (as written by the applicant)	• Generate human-scaled devices for implantation. • Quality control of devices according to physical properties. • Validate device performance with in vitro cell assays. • Validate device performance with in vivo implantation into swine, to simulate human engraftment.
Statement of Benefit to California (as written by the applicant)	The International Diabetes Federation has estimated that by 2035, the worldwide population of diabetics will be over 590 million; the worldwide market for diabetes treatments has been projected to reach $65 billion by 2020. The device undergoing final preclinical testing in large animals here provides an essential component to a cell therapy cure with a made-in-California product that can be manufactured locally for worldwide distribution.
Funds Requested	$172,984
GWG Recommendation	***Tier 2 – Not recommended for funding.***

Final Score: 64

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.

Median	65
Standard Deviation	5
Highest	75
Lowest	55
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (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?	4	7	3
Is the rationale sound?	1	9	4
Is the proposal well planned and designed?	0	13	1
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

- The rationale for producing and testing various design beta cell encapsulation devices is solid. However, better encapsulation techniques are needed for translational therapies to treat diabetes with beta-cells.

Concerns

- There is a significant lack of detail regarding the cell types and materials that will be used throughout the proposal.
- Processes for large scale manufacturing of membranes and the large preclinical model studies seem premature for the status of the project. The justification for these is poor.

- The cells to be used are not clearly described.
- Little detail, if any, about the beta cells is presented. None of the listed collaborators will provide beta cells for the project.
- The potential immune response is not addressed.
- The proposal lacks experiential details and seems premature.
- There are some concerns about clarity of writing. It is difficult to understand.
- There is a lack of detail of the experimental plans.

Additional Comments

- There is a need to present QC parameters to evaluate membranes.

Public Summary for DISC1-08906

Application #	DISC1-08906
Title (as written by the applicant)	Using patient-specific hiPSCs to generate engraftable immunocompatible neurovascular units & other well-vascularized multi-cell-type functional complexes for organ creation & repair
Research Objective (as written by the applicant)	Demonstrate that hiPSC-derivatives (combined with biomaterials) circumvent the challenges of organ replacement/reconstruction presently encountered by grafting fully-formed cadaveric organs.
Impact (as written by the applicant)	An alternative therapy for those (frequently wounded warriors) unable to obtain “vascularized composite allotransplants”, as well protocolizing 3D printing, & providing “bridges” to organ donation.
Major Proposed Activities (as written by the applicant)	• Generate engraftable neurovascular units & myoblasts from iPSCs in vitro layered upon biosynthetic scaffolds to observe the generation of large amounts of functional replacement skeletal muscle. • Implant & assess the functional consequences of a mixture of iPSC-derived myoblasts & neurovascular units layered upon PGLA scaffolds into the immunocompetent anterior tibialis excision mouse model.
Statement of Benefit to California (as written by the applicant)	Vascularized Composite Allotransplantation (VCA), which seeks to address the plight of veterans (a large CA contingency) left without functioning organs & limbs, has focused on grafting fully-formed cadaveric organs to recipients, presenting challenges: immunocompatability, availability, sub-optimal organ function. We speculate that derivatives from pluripotent stem cells (combined with biomaterials) generated from cells from the patient might circumvent these obstacles.
Funds Requested	$221,940
GWG Recommendation	***Tier 2 - Not recommended for funding***

Final Score: Below 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.

Median	---
Standard Deviation	---
Highest	---
Lowest	---
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (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?	1	11	2
Is the rationale sound?	0	12	2
Is the proposal well planned and designed?	0	13	1
Is the proposal feasible?	0	13	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

- No specific comments provided.

Concerns

- This is a very poorly written application that basically discusses ideas that might apply to the stem cell field. The overall ideas are not novel and are simply a somewhat futuristic look of where stem biology could go. While the long term outlook and the enthusiasm is appropriate, the application does not offer a reasonable path of bringing the future goals into focus and into a realistic approach.

- This application does not provide any structured research outline, contains no detailed description of the approach

and discusses no realistic timeline.

- The experiments are not outlined well.
- The research plan is overambitious (ie. muscle, bone, etc.).
- The concept of on demand autografts will not turn out to be clinically viable for the target patient population.
- The proposal is unlikely to deliver on the grandiose ideas.
- Despite the forward looking vision, the applicant proposes an outdated biomaterial approach.

Additional Comments

- No additional comments were expressed by the GWG.

Public Summary for DISC1-08910

Application #	DISC1-08910
Title (as written by the applicant)	Reprogramming human stem cells for blood cell generation
Research Objective (as written by the applicant)	To create a universal donor blood cell line that can be used to produce human red blood cells for transplantation.
Impact (as written by the applicant)	Successful completion of this work would create a safe, unrestricted source of universal donor human blood cells that could be used to improve healthcare and save lives throughout the world.
Major Proposed Activities (as written by the applicant)	• Aim 1: Development of a human donor blood cell line by introduction of the appropriate signals into stem cells • Aim 2: Induce the human donor blood cell lines to produce red blood cells
Statement of Benefit to California (as written by the applicant)	Because this research will lead to the development of methods to address the critical shortage of universal donor blood for transfusions, the State of California and its citizens will directly benefit. California-based military personnel stationed elsewhere will also benefit from this resource. Importantly, in emergency situations, it will not be necessary to obtain blood test results to identify the recipient's blood type, thus expediting access to treatment and improving patient outcomes.
Funds Requested	$232,200
GWG Recommendation	***Tier 2 – Not recommended for funding.***

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.

Median	85
Standard Deviation	4
Highest	90
Lowest	75
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	11
Tier 2 (1-84): Not recommended for funding	4

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?	7	1	7
Is the proposal well planned and designed?	5	3	7
Is the proposal feasible?	4	1	10

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 objective behind this proposal is based on providing cost-effective and safe blood for human transfusions. The production of blood cells on demand would directly translate into human applications.
- It is medically and highly advantageous if one could produce human blood from stem cells. Preliminary results with the critical gene in the proposal are strong
- Completion of the Specific Aims will produce a potential source of blood. This would be an outstanding and potentially life-changing outcome.

- The Principal Investigator (PI) has clearly thought about many of the potential issues that could arise during the proposed experiments and has proposed clear alternatives.

Concerns

- Although the proposed work has important implications for blood generation and the PI is excellent, concerns remain about the safety behind altering expression of the critical gene and the potential for leukemia.
- The proposed mouse models may not allow the PI to effectively test human erythroid lineage outcomes.

Additional Comments

- A lentiviral approach seems outdated; There are concerns about introducing integrating lentiviral DNA approaches, though this could be changed later.

Public Summary for DISC1-08913

Application #	DISC1-08913
Title (as written by the applicant)	Transcriptional profiling of human bioengineered kidney organoids and in vivo nephrons
Research Objective (as written by the applicant)	Identify normal programs of nephrogenesis within the human kidney to enable educated approaches to the in vitro engineering of normal kidney structures.
Impact (as written by the applicant)	Will establish an essential molecular and cellular benchmark for normal human nephrogenesis to inform and guide world-wide research efforts to model, treat and prevent human kidney disease.
Major Proposed Activities (as written by the applicant)	• RNA-seq analysis to generate transcriptional profiles underlying early segmentation and patterning of the human nephron using a MARIS RNA-isolation protocols and human kidney samples. • Generate and validate cell-type specific fluorescent reporter lines by Cas9-mediated targeting of human ESCs for the identification and isolation of key cell types from kidney organoids in vitro.
Statement of Benefit to California (as written by the applicant)	One in ten American adults suffer from Chronic Kidney Disease. Of these, 400,000 depend upon regular dialysis to replace kidney function. The rate of End Stage Renal Disease in California exceeds the national average by approximately 10%. The CIRM award will drive the development of replacement therapies to restore kidney function, the generation of kidney disease models for drug discovery, and improve on the efficacy of drug development by pre-screening against nephrotoxic compounds.
Funds Requested	$222,026
GWG Recommendation	***Tier 2 – Not recommended for funding.***

Final Score: 61

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.

Median	60
Standard Deviation	7
Highest	75
Lowest	50
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (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?	6	7	1
Is the rationale sound?	3	7	4
Is the proposal well planned and designed?	2	7	5
Is the proposal feasible?	5	5	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 cell lines generated in this study would be valuable to the field in generating and characterizing kidney organoids.
- Principal Investigator (PI) is extremely talented and is a very strong molecular biologist.

Concerns

- The proposal does not address how the RNAseq datasets would enable development of improved organoid models.
- The value of RNA seq dataset is not clear; RNA seq data analysis might need further description.

- What other RNA seq datasets are available? There needs to be more discussion in the context of available data.
- The proposed project is purely descriptive and not novel.

Additional Comments

- There have been publications of hPSC-derived kidney cell RNAseq datasets. This proposal represents an incremental advance rather than an innovative idea.
- This work has already been published by several groups, including one from the PI's group itself.

Public Summary for DISC1-08914

Application #	DISC1-08914
Title (as written by the applicant)	Human induced pluripotent stem cell-derived cardiomyocyte engraftment in a porcine myocardial infarction model.
Research Objective (as written by the applicant)	The objective of this study is to evaluate the engraftment of human stem cell-derived cardiac cells in the pig heart after heart attack and to determine the effect extracellular matrix on retention.
Impact (as written by the applicant)	If successfully realized, this research will lead to further studies capable of translating this technology for the treatment of human patients who have suffered from heart attacks.
Major Proposed Activities (as written by the applicant)	• To evaluate the ability of commercially-produced human stem cell-derived cardiac cells to engraft and survive in a large animal heart attack model. • To investigate the effect of supportive extracellular matrix on the engraftment and survival of transplanted human induced pluripotent stem cell-derived cardiac cells in the infarcted myocardium.
Statement of Benefit to California (as written by the applicant)	Heart failure as a result of acute myocardial infarction is a leading cause of morbidity and mortality in California. Discovering new therapies to reduce the burden of heart failure will not only improve the lives of Californians suffering from this disease. The goal of this study is provide preclinical data that will enable the use of stem cell-based therapies to treat acute myocardial infarction and heart failure.
Funds Requested	$221,441
GWG Recommendation	***Tier 2 – Not recommended for funding.***

Final Score: 76

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.

Median	75
Standard Deviation	3
Highest	80
Lowest	70
Count	13

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (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?	7	3	3
Is the rationale sound?	3	5	5
Is the proposal well planned and designed?	0	7	6
Is the proposal feasible?	1	10	2

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 strong translational potential with innovative cell delivery and matrix. The investigators have a strong history of translation.
- The choice of industry partner makes sense.
- The rationale of testing human iPS-cardiac myocytes in a large preclinical myocardial infarction model is important.

Concerns

- Experiments will be confounded by immune rejection, which very likely cannot be controlled as suggested.
- There is no need to test transcatheter injection first - surgical injection would be better controlled.
- The immunohistochemistry of unlabeled cells will be difficult.
- There is little detail, rationale and justification for the matrix.
- The rationale for Aim 1 is unclear; this experiment is just a control for ECM treatment in Aim 2

Additional Comments

- Matrix-enhanced vs. not matrix enhanced cell retention study - this should be done first in a nude mouse or rat model with genetically labelled cells to quantitatively assess cell retention.
- A higher throughput model (e.g. rodent) may be better to test engraftment and viability without cost and immune suppression issues associated with pig, since functional evaluation is not a key part of the project.
- Numerous studies suggest that cardiac progenitors may engraft better than fully differentiated cardiomyocytes.

Public Summary for DISC1-08933

Application #	DISC1-08933
Title (as written by the applicant)	Splicing Modulators as Leukemia Stem Cell Inhibitors in Acute Myeloid Leukemia
Research Objective (as written by the applicant)	The scientific objective is to determine if splicing disruption drives leukemia stem cell (LSC) generation in acute myeloid leukemia and if splicing modulation selectively impairs LSC maintenance.
Impact (as written by the applicant)	AML is generally incurable because of leukemia stem cell (LSC) driven relapse. Discovery of a LSC splice isoform signature and splicing modulator would inform LSC eradication trial development.
Major Proposed Activities (as written by the applicant)	• Whole transcriptome sequencing will be performed on hematopoietic stem and progenitor cells from human acute myeloid leukemia and age matched marrow to identify a LSC splice isoform signature. • Validation of the splice isoform LSC signature will be performed by splice isoform specific qRT-PCR and on a single cell level by Fluidgm to establish if there is clonal dominance. • Lentiviral over expression and shRNA knockdown of MBNL3, a repressor of embryonic alternative splicing, will be performed to in normal progenitors and LSC to determine if it regulates LSC splicing. • The LSC splicing inhibitory activity of splicing modulator, FD-895, will be compared with a pro-survival splice isoform switching inhibitor, Sabutoclax, in LSC stromal co-cultures by qRT-PCR. • The LSC inhibitory activity of FD-895 will be compared with Sabutoclax in stromal co-cultures and bicistronic FUCCI cell cycle assays. • The LSC inhibitory activity of FD-895 will be compared with Sabutoclax in humanized AML mouse models.
Statement of Benefit to California (as written by the applicant)	Acute myeloid leukemia is a devastating and rapidly fatal blood cancer that is largely incurable as a result of persistence of dormant leukemia stem cells that resist chemotherapy, epigenetic modifiers and tyrosine kinase inhibitors. Individuals who have had chemotherapy or radiation therapy for solid tumors or have myelodysplastic syndrome (MDS) or myeloproliferative neoplasms (MPNs) are at increased risk of developing therapy resistant AML.
Funds Requested	$150,000
GWG Recommendation	***Tier 2 – Not recommended for funding.***

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.

Median	85
Standard Deviation	4
Highest	90
Lowest	75
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	11
Tier 2 (1-84): Not recommended for funding	3

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	3
Is the rationale sound?	7	0	7
Is the proposal well planned and designed?	6	3	5
Is the proposal feasible?	5	4	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 nice preliminary data, as published, showing knockdown on on a key gene reversing the splice isoform program in CML.
- A testable molecule (17S-FD-895) could lead to a therapeutic.
- A nice, reasonably novel, hypothesis is presented.
- The proposal is clear and well written with an important target (selective LSC sensitivity).

- There are clear aims and a well supported rationale.

Concerns

- The proposal is overambitious, and concerns remain regarding feasibility.
- The proposed idea is in a very competitive and crowded space.
- Though the track record of the group is strong, it is unlikely the team will reach the goal in two years.
- Much of the previous data is derived from CML rather than AML, and their relevance to AML, particularly secondary AML, is unclear.

Additional Comments

- No relevant comments were expressed by the GWG.

Public Summary for DISC1-08940

Application #	DISC1-08940
Title (as written by the applicant)	Development of a Novel Human Neural Cell Based Drug Screening and Neurotoxicity Evaluation Platform Using iPSC Directly Differentiated Neural Cells.
Research Objective (as written by the applicant)	To further develop and validate our iPSC-based neural co-culture platform in order to meet the requirements for applications of drug development and neurotoxicity testing.
Impact (as written by the applicant)	High attrition rates in drug development are partially due to poor prediction of mouse models. Our new neural in vitro platform should be able to assess disease phenotypes in a human relevant context.
Major Proposed Activities (as written by the applicant)	• Different compositions of neural cell types will be tested to find the optimal neural co-culture mixture for identifying a broad range of neurotoxicity effects and disease phenotypes. • Optogenetic tools will be implemented for selective inhibition or activation of specific neuronal subpopulations in order to include functional parameters in the analyses of complex phenotypes. • A particular neurologic disorder phenotype will be induced via 3 different approaches in iPSC-derived neural co-cultures in order to test the platform performance for disease modeling and drug screens. • A set of test compounds with well-described neuroactive effects and a control set will be analyzed to assess the predictive performance of our neural co-culture platform for neurotoxicity testing.
Statement of Benefit to California (as written by the applicant)	As a biotech startup we are confronted with the financial constraints of a small business. This grant will allow us to hire new personnel to solely focus on R&D. The creation of skilled well paid jobs is vital for the economic growth of California. This project will focus on developing a novel drug discovery platform for neural related diseases. This innovation will not only generate IP that will help our company grow but has the possibility of helping patients with neurological disorders.
Funds Requested	$202,500
GWG Recommendation	***Tier 2 – Not recommended for funding.***

Final Score: Below 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.

Median	---
Standard Deviation	---
Highest	---
Lowest	---
Count	13

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (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?	3	8	2
Is the rationale sound?	1	8	4
Is the proposal well planned and designed?	0	11	2
Is the proposal feasible?	1	10	2

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 a clear need for human models in drug development.

Concerns

- There is insufficient recognition of the high level of complexity in the project. The proposal is overly ambitious, and analytic choices are poorly justified.
- There is questionable infrastructure; it is unclear whether the company’s infrastructure can successfully handle this project.

- The use of microelectrode array (MEA) analysis has been pursued for some time already and is not novel.
- The goal should be the validation of the model with a focus on neurotox. Since the system has not been fully fleshed out, there is no reason to use optogenetics.
- The argument that it is potentially valuable to use neuron-related populations that are not fully differentiated is unsupported. In addition, these cells have no clear counterparts in the developed nervous system.
- The ideas about astrocytes are naïve in the sense that there are multiple types of astrocytes with different properties.
- As a service for pharma, this looks very weak as a primary platform for a company.

Additional Comments

- The Principal Investigator is very junior.
- There are lots of people using cell cultures for toxicity screening.