$25,507,913 GWG RECOMMENDED | Score Range | Number of GWG Votes

APP #	TITLE	BUDGET REQ	SCORE (MEDIAN)	Mean	SD	Low	High	Fund?	Y	N	Resubmitted Application?	Applicant Received Previous CIRM Funding?	Disease/Technology Indication	Product Type	Approach	Number of active projects, approved funding ($) and approaches by stage for indication/use
DISC2-09526	GENE EDITING FOR FOXP3 IN HUMAN HSC	$1,100,568	95	93	3	85	95	Y	15	0	Y	N	IPE (immunodysregulation polyendocrinopathy enteropathy) X-linked syndrome	Gene-modified cell therapy	CRISPR/Cas9 edited autologous HSC	None
DISC2-09649	A treatment for Zika virus infection and neuroprotection efficacy	$2,117,880	93	93	3	85	100	Y	15	0	N	Y	Zika	Small molecule	Repurposing FDA-approved anti-viral for neuroprotection	None
DISC2-09565	Preclinical development of human hepatocyte progenitor cells for cell therapy	$1,655,436	90	91	1	90	95	Y	15	0	N	Y	Liver diseases	Cell therapy	In vitro expansion of hepatocyte progenitor cells for liver regeneration	0 CLIN & TRAN STAGE 7 DISC STAGE ($12.7M): • iPSC, ESC derived cells and organoids • Gene modified PSC derived cells • Endothelial progenitor cells • Direct reprogramming
DISC2-09615	Targeted off-the-shelf immunotherapy to treat refractory cancers	$2,134,868	90	91	2	88	95	Y	15	0	N	N	Cancer (solid & hematologic)	Gene-modified cell/Immunotherapy	Allogeneic iPSC derived CAR NK cells	5 CLIN STAGE ($61.1M): • ICT-107 autologous dendritic cells • Autologous gene-modified HSC • Biologics (Cirmtuzumab, anti-CD47 Ab) • Small molecule PLK4 inhibitor 2 TRAN STAGE ($9.9M): • Autologous Lenti/iNKT-sr39TK modified HSC (iNKT) • Peptide-KLH vaccine 7 DISC STAGE ($13.1M): • iPSC derived T-cells • Anti-CSC Ab biologics • Cancer mechanism studies
DISC2-09569	hNSC-mediated delivery of ApiCCT1 as a candidate therapeutic for Huntington's disease	$1,787,543	90	90	2	84	94	Y	13	1	N	Y	Huntington's disease	Gene-modified cell & biologic therapy	hESC-derived hNSCs expressing secreted ApiCCT1	0 CLIN STAGE 1 TRAN STAGE ($5.0M): • Allogeneic ESI-017 ESC derived Neural Stem Cells 0 DISC STAGE
DISC2-09624	Protein tyrosine phosphatase - sigma inhibitors for hematopoietic regeneration	$2,116,708	90	90	3	85	95	Y	14	0	N	Y	Regenerating blood/immune system after myelo-ablation/suppression	Small molecule	Small molecule PTPσ inhibitors for hematologic recovery	2 CLIN STAGE ($19.1M): • AB-110 cord blood HSC and gene modified endothelial cells • Biologic anti-CD117 Ab 0 TRAN STAGE 1 DISC STAGE ($5.2M): • Blood stem cell growth factors
DISC2-09596	Direct Cardiac Reprogramming for Regenerative Medicine	$2,400,048	88	88	4	85	95	Y	14	0	N	Y	Heart failure	Gene therapy	In vivo delivery of cardiac reprogramming factors for cardiac regeneration	3 CLIN STAGE ($42.2M): • Allogeneic cardiosphere derived cells • Allogeneic ESC derived CM 0 TRAN STAGE 11 DISC STAGE ($19.4M): • Cell therapies (PSC derived CM, adult cardiac cells) • Exosomes (sources - adult cardiac tissue, iPSC) • Tissue engineering • Scar reducing biologic • Preclinical animal modeling • Manufacturing process development
DISC2-09635	Designing a cellular niche for transplantation of human embryonic stem cell-derived beta cells	$2,006,076	88	88	3	85	93	Y	15	0	Y	N	Type 1 Diabetes	Cell therapy	Allogeneic hESC derived engineered islets	3 CLIN STAGE ($30.2M): • VC-01/02 hESC derived pancreatic cells in encapsulation device 1 TRAN STAGE ($5.0M): • Genetically matched stem cell derived islets 0 DISC STAGE
DISC2-09559	Thin Film Encapsulation Devices for Human Stem Cell derived Insulin Producing Cells	$1,092,063	87	87	4	80	90	Y	13	2	N	N	Type 1 Diabetes	Cell & device combo therapy	Thin film device with allogeneic hESC derived beta cells	3 CLIN STAGE ($30.2M): • VC-01/02 hESC derived pancreatic cells in encapsulation device 1 TRAN STAGE ($5.0M): • Genetically matched stem cell derived islets 0 DISC STAGE
DISC2-09610	CRISPR/dCas9 mutant targeting SNCA promoter for downregulation of alpha-synuclein expression as a novel therapeutic approach for Parkinson's disease	$1,931,589	85	87	7	75	100	Y	11	4	Y	Y	Parkinson's disease	Gene therapy	CRISPR/dCas9 editing of alpha-synuclein	0 CLIN AND TRAN STAGE 3 DISC STAGE ($4.8M): • Autologous iPSC derived DA neurons • Patient Derived iPSC disease modeling • Biomaterial systems for cell manufacturing and delivery
DISC2-09631	Identification and characterization of the optimal human neural stem cell line (hNSC) for the treatment of traumatic brain injury (TBI).	$1,557,203	85	87	10	65	100	Y	9	5	N	Y	Traumatic brain injury	Cell therapy	Efficacy comparison of 4 GMP neural stem cell products	None
DISC2-09542	Multipotent Cardiovascular Progenitor Regeneration of the Myocardium after MI	$1,399,839	85	85	4	80	90	Y	9	5	N	Y	Heart failure	Cell therapy	iPSC derived cardiac progenitor cells	3 CLIN STAGE ($42.2M): • Allogeneic cardiosphere derived cells • Allogeneic ESC derived CM 0 TRAN STAGE 11 DISC STAGE ($19.4M): • Cell therapies (PSC derived CM, adult cardiac cells) • Exosomes (sources - adult cardiac tissue, iPSC) • Tissue engineering • Scar reducing biologic • Preclinical animal modeling • Manufacturing process development
DISC2-09637	Genome Editing to Correct Cystic Fibrosis Mutations in Airway Stem Cells	$2,201,136	85	85	3	80	90	Y	10	5	N	Y	Cystic fibrosis	Gene-modified cell therapy	CRISPR/Cas9 edited autologous airway epithelial stem cells	None
DISC2-09460	Microenvironment for hiPSC-derived pacemaking cardiomyocytes	$2,006,956	85	80	17	20	86	Y	9	6	Y	Y	Cardiac arrhythmia	Cell therapy	iPSC derived pacemaker cardiomyocytes	0 CLIN AND TRAN STAGE 2 DISC STAGE ($7.7M): • iPSC derived pacemaker CM • small molecule drug (LQTS Type 3)
DISC2-09645	Dynamic scaffolding system to enhance lineage-specific differentiation and downstream functionality of induced pluripotent stem cells	$804,254	84	83	5	75	90	N	7	8						
DISC2-09396	Targeted Gene Therapy in the Treatment of X-Linked Hyper-IgM Syndrome	$1,656,548	83	83	3	80	92	N	7	8						
DISC2-09592	Real-time monitoring of stem cell differentiation for quality assurance in regenerative medicine applications	$1,100,568	80	79	6	65	89	N	4	11						

APP #	TITLE	BUDGET REQ	SCORE (MEDIAN)	Mean	SD	Low	High	Fund?	Y	N	Resubmitted Application?	Applicant Received Previous CIRM Funding?	Disease/Technology Indication	Product Type	Approach	Number of active projects, approved funding ($) and approaches by stage for indication/use
DISC2-09617	iPS Glial Therapy for White Matter Stroke and Vascular Dementia	$2,080,925	80	78	5	69	84	N	0	15						
DISC2-09505	Human Heart-on-a-Chip for Disease Modeling and Developing New Strategies to Treat Cardiac Diseases	$1,096,843	75	78	4	75	85	N	1	14						
DISC2-09510	Stem cell-derived exosomes to ameliorate radiation-induced cognitive dysfunction	$1,398,793	75	76	5	70	84	N	0	14						
DISC2-09501	Micro-scale Energy and Chemical Systems (MECS)-based iPSC-Bioartificial Liver device.	$798,800	75	75	4	70	80	N	0	15						
DISC2-09601	Stem cell enabled development of a therapeutic candidate against Huntington's Disease	$1,130,616	70	73	6	60	85	N	1	14						
DISC2-09567	Integration-defective lentiviral vector-mediated gene editing in human pluripotent stem cells	$1,042,694	75	71	5	60	75	N	0	15						
DISC2-09400	Mechanical Activation of Adipose-Derived Stem Cells for the Prevention and Treatment of Diabetic Foot Ulcers Using a Novel CD-Microfluidic Device	$1,723,910	65	66	6	50	75	N	0	14						
DISC2-09536	The Synthetic Notch Receptor as a Tool for Spatially Targeting Stem Cell Differentiation and Regeneration	$1,113,000	--	--	--	--	--	N	0	15						
DISC2-09500	Zika virus-induced disturbances in human neural stem cells: from mechanisms to therapeutics	$1,064,755	--	--	--	--	--	N	0	15						
DISC2-09585	Treating Duchenne muscular dystrophy with Cas9 based gene editing of satellite cells.	$2,117,166	--	--	--	--	--	N	0	15						
DISC2-09654	Discovery of therapeutics for Huntington's Disease	$1,399,800	--	--	--	--	--	N	0	15						
DISC2-09656	Direct Reprogramming of fibroblasts into myogenic cells by using chemical compounds	$2,132,926	--	--	--	--	--	N	0	15						
DISC2-09627	Neural Stem Cell Delivery of Oncolytic Virus for Targeted Treatment of Ovarian Cancer Metastases	$1,757,793	--	--	--	--	--	N	0	15						
DISC2-09391	Development of small molecule inhibitors of stress granule formation as a treatment for ALS	$2,071,300	--	--	--	--	--	N	0	15						
DISC2-09602	Recovery of brain function by mitochondria transfer from stem cells to injured neurons	$823,700	--	--	--	--	--	N	0	15						
DISC2-09633	Human embryonic stem cell-derived satellite-like cells to treat respiratory insufficiency in children with severe and intermediate congenital NEM	$1,718,500	--	--	--	--	--	N	0	14						
DISC2-09473	Targeting Migrating Glioblastoma Stem Cells Through ETV6	$2,129,700	--	--	--	--	--	N	0	15						

DISCOVERY

Application #	DISC2-09391
Title (as written by the applicant)	Development of small molecule inhibitors of stress granule formation as a treatment for ALS
Research Objective (as written by the applicant)	Using an in vitro assay based on motor neurons generated from human induced pluripotent stem cells, we propose to develop drug candidates for disease-modifying therapy of ALS (Lou Gehrig's disease).
Impact (as written by the applicant)	We will impact two bottlenecks in the development of treatments for ALS: the lack of disease-relevant in vitro assays and the paucity of new molecular entities entering the drug discovery pipeline.
Major Proposed Activities (as written by the applicant)	• Hit confirmation 1: Synthesize quinacrin and perfluridol analogs and test these in the G3BP1-GFP stress granule assay in control iPSC-derived motor neurons in dose-response. • Hit confirmation 2: Test quinacrin and perfluridol analogs in mutant (TDP-43, FUS/TLS, hnRNP A2/B1) iPSC-derived motor neurons for the reduction of stress granules and extension of long-term survival. • Hit expansion 1: Synthesize elaborated analogs, test these in cellular stress granule and long-term survival assays and identify structure-activity relationships (SAR) and critical pharmacophores. • Hit expansion 2: Test high affinity analogs in in vitro DMPK assays for solubility, permeability, P-gp efflux, microsomal stability, plasma binding and brain tissue binding. • Lead optimization 1: Resynthesize lead compounds with favorable in vitro profiles on larger scale for evaluation in vivo and conduct formulation and bioavailability studies. • Lead optimization 2: Determine in vivo pharmacodynamics/pharmacokinetics and brain penetration, and multi-dose tolerability of lead compounds.
Statement of Benefit to California (as written by the applicant)	Amyotrophic lateral sclerosis (ALS) is an invariably fatal motor neuron disease that afflicts ca. 30,000 Americans, of which an estimated 3000 live in California. Treatment options are extremely limited. Our proposed research will advance promising new drug candidates through late-stage preclinical testing. The proposed studies are to be performed in California, thereby creating job opportunities and income for California citizens.
Funds Requested	$2,071,300
GWG Recommendation	***Tier 2: Not recommended for funding***

Scoring Data

Final Score: --

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

Mean	--
Median	--
Standard Deviation	--
Highest	--
Lowest	--
Count	--
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?	1	9	5
Is the proposal well planned and designed?	1	10	4
Is the proposal feasible?	4	8	3

Reviewer Comments

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

Strengths

- *None noted.*

Concerns

- The case that stress granules are of pathogenic importance, as contrasted with being a consequence of other pathology, remains poorly made. It is recognized the applicant believes passionately in this hypothesis, but convincing data needs to be provided - which means doing the in vivo experiment.
- It may be that stress granules contribute to ALS, even though it is not proven. So an effort to design a therapy based on a stress granule assay might lead to something useful. This reviewer is equivocal about the need for urgency versus the need for economical timing of a start of a study like this.
- The proposal is based on the hypothesis that stress granules are the pathological entity in ALS motor neuronal failure. However, according to a cited review stress granules and the associated RNA and RBPs are identifiable but to date the complexes have not been isolated and it is not clear how and whether they contribute to disease pathology.
- There is a sense that stress granules may be causative. Multiple different genes when defective cause stress granule accumulation AND disease, so it becomes somewhat plausible there is a connection. But there seems to be more work to be done in this field to make this connection robust.
- Causation of stress granules in ALS is overstated. For examples, editing of GluR2 is impaired in ALS motor neurons, which can cause excessive calcium influx and death. Abnormal editing of EAAT2 is also a hallmark of ALS neurons. However, it might be reasonable to use stress granules as a readout for drug screening.
- Applicant provided data showing that inhibition of stress granules affected motor neuron survival but this was not conducted using relevant patient derived cells.
- Previous reviews focused on whether stress granules were the cause or result of pathology. If they are the result of pathology, then interventions designed from a reduction in stress granule assay might not be relevant.
- The current proposal still does not make a convincing argument that stress granules cause pathology. That said, even if stress granules do not cause ALS, a small molecule that reduces stress granules might also inhibit ALS if it happened to act sufficiently upstream of the mutually causative event.
- This reviewer would prefer to see more evidence that stress granules contribute to or cause ALS before investing into an effort predicated on that knowledge.
- The clinical development of the drug is not well-described.
- The analysis of the drugs on neuronal function is proposed as the last activity. This should be the priority of the proposal before more drug screening is proposed and drug optimization is conducted.
- The refusal of the applicant to use their lead drug in vivo is not understandable. If the claim is made that a lead drug is in hand, then it is mandatory to do the in vivo experiment. This is especially the case as the success record in ALS has been dismal despite a great deal of excellent and interesting science.
- Survival remains the only readout of the drug, which is inadequate considering the many clinical failures of drugs that have been shown to extend in vivo survival of motor neurons from a variety of ALS relevant stressors.
- No functional readout to prove feasibility even though they have all the tools as a result of previous funding to perform the experiments. Key results from key experiments showing efficacy of the drug are needed before resubmission.
- The applicant received two other CIRM grants to develop the drugs and has still not provided any functional efficacy beyond survival time. The overall proof of concept is still not achieved.

- The PI has mixed performance on previous CIRM grants. On the one hand, very few milestones on these grants were completed. On the other hand, a patent and several publications resulted.
- Overall the design is solid, however, only a small percentage of cells present with protein inclusions. Thus, homogeneity of cultures remains an issue.
- The two references in the application to Liu-Yesucevitz et al papers from 2010 and 2011 are not terribly convincing, nor is a review of the more recent literature via PubMed (eg., PMID: 24555412 from 2014 or PMID: 26557057 from 2015).

Additional Comments

- Please pay attention to reviewers' past comments.

DISCOVERY

Application #	DISC2-09396
Title (as written by the applicant)	Targeted Gene Therapy in the Treatment of X-Linked Hyper-IgM Syndrome
Research Objective (as written by the applicant)	We are seeking to develop site-specific hematopoietic stem cell gene therapy with autologous transplant as a definitive treatment option for X-linked Hyper-IgM Syndrome.
Impact (as written by the applicant)	These studies would bring stem cell gene therapy for X-HIGM closer to the clinic, as there are currently no options for those without an HLA match or with infections too severe for allogeneic HSCT.
Major Proposed Activities (as written by the applicant)	• Define the optimal CRISPR/Cas9 and corrective donor template targeting CD40 Ligand with the highest efficiency and specificity and minimal effects on hematopoietic stem cell viability. • Evaluate the efficacy of optimized genome-editing reagents in hematopoietic stem cells in vitro and in vivo. • Assemble the planned draft clinical protocol, pre-clinical activity and toxicology studies, and the pharmaceutical quality/CMC in preparation for a pre PRE-IND meeting with the FDA.
Statement of Benefit to California (as written by the applicant)	Safe, definitive therapies for X-Linked Hyper-IgM Syndrome represent an unmet medical need. Allogeneic hematopoietic stem cell transplant is frequently complicated by graft-versus-host disease and worsening of pre-existing infections. Successful demonstration that stem cell gene therapy can safely and effectively address X-HIGM will shift the paradigm by which patients in California will be treated. This will lead to improved patient care and influence treatment for patients around the world.
Funds Requested	$1,656,548
GWG Recommendation	***Tier 2: Not recommended for funding***

Scoring Data

Final Score: 83

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

Mean	83
Median	83
Standard Deviation	3
Highest	92
Lowest	80
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?	10	2	3
Is the rationale sound?	6	5	4

DISCOVERY

Is the proposal well planned and designed?	6	3	6
Is the proposal feasible?	6	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

- Important biological question.
- High potential for success.
- Good system for testing a gene editing technology.
- The system uses state of the art methods.
- This would be a good model to demonstrate gene correction therapy. It has a chance of working.
- Bone marrow transplant is a therapeutic option, but it would be nice to see it replaced with a better therapy such as this.

Concerns

- The need for the treatment may be questionable.
- The first two milestones appear to be achievable, the third seems ambitious.
- Task 3 is the main weakness.
- It is not novel as a paper has been recently published in Blood journal on this topic.
- Need to survey the competitive landscape and differentiate from other groups (potentially those with more experience) that may be doing similar things.
- Novelty of approach is lacking.
- PI is a new investigator. It is questionable whether she is ready to lead such a complex project.
- Disease is very rare, and so broad population morbidity/mortality impact is low.
- Need to clarify why the project is switching from TALENs to CRISPR technology.
- It is unclear why the TALEN approach is not being pursued.
- Great data with TALEN, why not doing a trial with TALEN instead of CRISP/Cas9?

Additional Comments

Needs to improve grantsmanship (summary reads as review on gene editing).

DISCOVERY

Application #	DISC2-09400
Title (as written by the applicant)	Mechanical Activation of Adipose-Derived Stem Cells for the Prevention and Treatment of Diabetic Foot Ulcers Using a Novel CD-Microfluidic Device
Research Objective (as written by the applicant)	We plan to identify the optimal parameters needed to produce a fat-based stem cell therapeutic that can be used for the prevention and treatment diabetic foot ulcers.
Impact (as written by the applicant)	Diabetic foot ulcers are the leading cause of nontraumatic lower limb amputations and treatment options are severely limited. We are developing a therapeutic will save limbs and ultimately lives.
Major Proposed Activities (as written by the applicant)	• We will use our novel fat processing device to demonstrate that we can increase the activity of stem cells that reside diabetic fat tissue, but are inherently limited in function. • We will use cutting edge profiling techniques to identify the processing parameters that yield the most potent therapeutic to prevent and heal the diabetic foot ulcer, but is also safe for the patient. • Once we identify the parameters that produce the most effective therapeutic, we will use basic science laboratory techniques to demonstrate the regenerative properties of this therapeutic. • The therapeutic will be combined with fat at different ratios and reinjected in mice to determine the best formulation of our therapeutic needed to prevent the formation of the diabetic foot ulcer. • We will prove that mechanical processing of diabetic fat tissue creates a safe and effective therapeutic for the prevention of diabetic foot ulcer formation in an animal model. • We will prove that mechanical processing of diabetic fat tissue creates a safe and effective therapeutic for the treatment of diabetic foot ulcer formation in an animal model.
Statement of Benefit to California (as written by the applicant)	More than any other state, California has the greatest number of new cases of diabetes annually. nearly 4 million Californians have diabetes and a staggering 1.5 million of these individuals are undiagnosed. Unfortunately, 30% of individuals who go untreated will require a lower extremity amputation and a staggering 50% will die within 5 years of having this surgery. We are developing a safe and effective therapeutic that will save limbs, and ultimately save lives
Funds Requested	$1,723,910
GWG Recommendation	***Tier 2: Not Recommended for funding***

Scoring Data

Final Score: 65

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

Mean	66
Median	65
Standard Deviation	6
Highest	75
Lowest	50
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0

DISCOVERY

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	3	6
Is the rationale sound?	0	9	5
Is the proposal well planned and designed?	1	9	4
Is the proposal feasible?	1	6	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

- Important problem.

Concerns

- May be too ambitious and not appropriate for this grant program.
- There is no specific reason why DFU is targeted for stem cell therapy using the technique described in the proposal.
- The stem cells in the proposal have been shown in the mouse model to aid in repair, but not for DFU.
- No evidence for the approach to help in diabetic foot prevention/treatment. No functional data on the proposed product.
- No evidence that stem cells can actually heal the ulcers.
- Preliminary data are provided to show that nanofat processing up-regulates stem cell markers and enriches processed fat for different stem cell populations, including MSCs, EPCs, ADSCs but no functional data on DFU are provided (only references on skin wrinkles treatment).
- Preliminary data are provided that applying shear forces to lipoaspirate by flowing it in a microfluidic device using a syringe pump (Fig. 4,5) and even better using centrifugation (Fig. 7,8) increases the fraction (enriches the fat of) MSCs, EPCs, ADSCs but no functional data on DFU are provided.
- Overall, preliminary data show enrichment of SCs (though no statistically significant differences are indicated, may require higher n of patients) but functional data about the effects of fat processing on the regenerative potential and/or the immunoregulatory properties of processed vs. control unprocessed fat is not shown.
- Lack of functionality with the cells.
- Functionality of diabetic cells may be compromised; outcome measures not well-defined.
- No evidence that the cells can function in the harsh diabetic wound environment.
- No details on microchip design and how to vary design to vary shear forces applied to processed fat, especially when comparing the Syntrfuge to the syringe pump-operated systems.
- Animal experimental groups are not outlined, just the total number of animals requested.
- The proposed STZ-treated B6 mice is not the most reliable mouse model to study diabetic wound healing. The db/db mouse model would have been more appropriate, especially with the wound healing model proposed in the approach.

DISCOVERY

Application #	DISC2-09460
Title (as written by the applicant)	Microenvironment for hiPSC-derived pacemaking cardiomyocytes
Research Objective (as written by the applicant)	This proposal investigates the effects of the microenvironment on the development and maintenance of pacemaking function in human induced pluripotent stem cell (hiPSC)-derived cardiomyocytes.
Impact (as written by the applicant)	Pacemaking function of hiPSC-derived cardiomyocytes is lost over time. Sustainability of pacemaking function of these cells is critical for engineering an biopacemaker from the patient's own cells.
Major Proposed Activities (as written by the applicant)	• Determine the effects of matrix scaffolds on the differentiation and maintenance of pacemaking function in hiPSC-derived cardiomyocytes. • Determine the appropriate hiPSC-derived cardiac cells to be subjected to the microenvironment for efficient yield of pacemaking hiPSC-derived cardiomyocytes. • Induce vascularization in tissue constructs in small animals to sustain pacemaking tissue construct. • Test sustainability of a functional pacemaking tissue construct in a small animal model.
Statement of Benefit to California (as written by the applicant)	Over 350,000 patients a year in the U.S. require an electronic pacemaker to restore their heart rhythm. The annual healthcare burden amounts to $20 billion. Repeated surgeries to replace battery and electrical parts generate additional costs and suffering for the patients. A biopacemaker engineered from human stem cell-derived pacemaking cells can overcome problems associated with electronics and improve the quality of life for the pacemaker recipient while reducing cumulative health care costs.
Funds Requested	$2,006,956
GWG Recommendation	***Tier 1: Recommended for funding***

Scoring Data

Final Score: 85

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

Mean	80
Median	85
Standard Deviation	17
Highest	86
Lowest	20
Count	15
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	9
Tier 2 (1-84): Not recommended for funding	6

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence

DISCOVERY

Does the proposal have a potential for impact?	7	6	2
Is the rationale sound?	9	4	2
Is the proposal well planned and designed?	10	3	2
Is the proposal feasible?	9	3	3

Reviewer Comments

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

Strengths

- There is a medical need for such studies.
- Well-written and focused grant with clear and defined milestones.
- Integrating scaffold and cells is a novel approach with potential for personalized medicine.
- The strength of this proposal is the novelty of using extracellular matrix to drive differentiation and maintenance of sinoatrial node cells.
- The preliminary data is strong.
- The use of large animals is an important step towards translation.
- The long-term testing is a major strength.

Concerns

- Do we need a biological alternative to device pacemakers?
- It is difficult to rationalize the cost of stem cell therapy for this indication when the mechanical options provide effective, economical care.
- There are several new advances with wireless pacing and biosensors that provide both sensing and remote monitoring; these will soon be coming to the clinic for extremely inexpensive costs to the healthcare system.
- The design provides good direction in examining this strategy. However, there is difficulty visualizing how such an approach would be cost-effective over the present therapy of a mechanical pacemaker, particularly since new technological developments with wireless technology are being developed.
- Not clear that this approach has a likely path to clinical translation. Concerns are that the cells need to overcome a lot of critical steps before being a pacemaker in vivo.
- Overall the feasibility of this technology seems low and cost prohibitive to present cost of medical care without having substantive advantages.
- While interesting scientifically, its application would require significant scale up from the patient's own cells before being useful; how would this be applied to patients who require a pacemaker urgently?
- Translational aspects are questionable even if cells acquire a pacemaker phenotype; is it really a true pacemaker phenotype? More sophisticated characterizations may be needed.
- Technology has many layers of complexity including targeting, persistence, and coordinated effort.

Additional Comments

- This resubmission is highly responsive to previous reviews.

DISCOVERY

Application #	DISC2-09473
Title (as written by the applicant)	Targeting Migrating Glioblastoma Stem Cells Through ETV6
Research Objective (as written by the applicant)	Migrating GBM are this cancer's stem cell, causing fatal and universal GBM recurrence, and expressing stem cell and fetal astrocyte genes. Targeting migrating GBM will improve survival.
Impact (as written by the applicant)	Treatments for GBM have not improved because little is known about the genetic characteristics of migrating GBM stem cells. Targeting migrating GBM will prevent disease progression.
Major Proposed Activities (as written by the applicant)	• To determine the extent to which migrating glioblastoma have consistent gene expression across patients. • To determine the extent to which primary human glioblastoma astrocytes depend upon stem cell genes for survival. • To test whether glioblastoma survival can be halted through targeting of migrating glioblastoma stem cell genes.
Statement of Benefit to California (as written by the applicant)	Even with complete surgical resection glioblastoma (GBM) the tumor universally and rapidly recurs. The aggressive invasion of surrounding brain contributes significantly to the poor prognosis (median survival <15 months), and little is known about the characteristics of these migrating GBM cells. GBM cells hijack the neurogenesis highways used by fetal brain precursor cells to disseminate throughout the brain. Targeting migrating tumor cells would substantially improve patient survival.
Funds Requested	$2,129,700
GWG Recommendation	***Tier 2: Not recommended for funding***

Scoring Data

Final Score: --

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

Mean	--
Median	--
Standard Deviation	--
Highest	--
Lowest	--
Count	15
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	8	2
Is the rationale sound?	1	12	2
Is the proposal well planned and designed?	2	11	2

DISCOVERY

Is the proposal feasible?	1	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 of a unique migratory population in GBM that can be identified and targeted would be a major advancement in the field.

Concerns

- A central problem in GBM is that by the time the patient comes to the clinic tumor cells have already migrated extensively. Even if every idea in this application was right this would still be a major challenge to a therapy that focuses on migration.
- There is no product.
- The likelihood that this will impact the clinical care of GBM is low.
- Not enough preliminary data to support rationale. Questions about clinical benefit: blocking cell migration after the cells have migrated would not benefit the clinical outcome.
- The proposal is totally focused on a subset of cells that are part of the GBM tumor mass that express an astrocytic phenotype. Thus, all other cell types are ignored.
- The applicant assumes that the astrocytes are the major and defining migratory cell population that define the invasiveness of the GBM. This assumption is not well-supported by data.
- The applicant proposes that GBM "most likely originate from astrocytes". This assumption is not supported by data.
- The target, ETV6, is not demonstrated to be necessary for GBM cell function.
- The focus on the molecule ETV6 is not well rationalized. ETV6 is only marginally increased in GBM cells compared to normal astrocytes and per their own published data ETV6 is not particularly highly expressed in embryonic astrocytes. In fact, ETV6 is not even listed as an embryonic astrocytic marker.
- The preliminary data are not compelling. The applicant only shows that loss of ETV6 in a single GBM cell line increases cell death and upregulates IL-6.
- The application includes in vivo analysis of one of their proposed unregulated genes, but whether this gene would be a drug target, how the drug could be delivered, what potential side effects the drug would have and how long it would take to develop a therapy are all not discussed.
- There is no evidence that ETV6 is a drugable target.

DISCOVERY

Application #	DISC2-09500
Title (as written by the applicant)	Zika virus-induced disturbances in human neural stem cells: from mechanisms to therapeutics
Research Objective (as written by the applicant)	Discover how Zika virus leads to brain defects in unborn fetuses to infected pregnant mothers by studying fetal-like brain stem cells and their protein machinery. Develop technologies to find drugs.
Impact (as written by the applicant)	No treatment exists for Zika virus. By testing human brain stem cells with Zika we propose to identify specific protein defects and discover potential drugs for treating brain-related birth defects.
Major Proposed Activities (as written by the applicant)	• Create brain (neural) stem cells and mini-brains in a dish from powerful embryonic-like pluripotent stem cells and then study how Zika blocks these stem cells from dividing and making new neurons. • In a developing brain, neural stem cells need travel from their birthplace to their final position in the brain. Here we will study how Zika targets and disrupts the movement of brain stem cells. • Assess how Zika targets the cell division (mitosis) process as brain stem cells make new neurons, requiring complex protein machinery (centrosome) to closely coordinate the dynamics with chromosomes. • Determine how Zika modifies the function of brain stem cell proteins involved in movement and maintaining DNA integrity, by tagging them with a phosphorylation mark, and use this to discover drugs. • Develop a method and discover new compounds that target and rescue the movement (migration) abnormalities of brain stem cells disrupted by Zika virus. • Develop an automated method for counting centrosomes during mitosis in brain stem cells and discover new compounds that normalize the centrosomes disrupted by Zika virus.
Statement of Benefit to California (as written by the applicant)	Almost 20,000 cases of Zika virus outbreak have been reported in the U.S., including 1,700 pregnant women, 18 live-born infants with birth defects (2 in California), and 5 pregnancy losses. Although 224 travel-related infections have been reported in California, local mosquito-borne transmission could spread here. This is a sobering reminder for Californians that ZIKV can cause serious harm to a developing fetus. Therefore, studying ZIKV now and discovering a treatment has become imperative.
Funds Requested	$1,064,755
GWG Recommendation	***Tier 2: Not recommended for funding***

Scoring Data

Final Score: --

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

Mean	--
Median	--
Standard Deviation	--
Highest	--
Lowest	--
Count	15
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0

DISCOVERY

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?	3	8	4
Is the rationale sound?	1	8	6
Is the proposal well planned and designed?	1	12	2
Is the proposal feasible?	2	7	6

Reviewer Comments

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

Strengths

- There is an urgent need to increase understanding of basic Zika biology, particularly in the context of human neurons. This proposal would address that need.
- A lot of really good data would be gathered, that could be generally useful if made broadly available to Zika researchers.

Concerns

- This is primarily a basic biology proposal and not appropriate for this program.
- This is a basic research grant that is focused on understanding the mechanics by which Zika affects brain development. The discussion of how this approach would be used to inform a therapeutic target is weak.
- Knowledge-generation basic science grant that lacks strong computational biology. Not clear what the target and the translation and long-term goal would be.
- While it is appreciated that the progression of this project might depend on understanding the initial defect that is caused by Zika infection, the applicant should discuss what stage of infection the research is targeting. Is the outcome targeted to the pregnant mother after diagnosis of Zika, for children born with microcephaly or for "normal" children who might develop a future defect?
- The team is strong in iPSCs, Zika, and proteomics. However, there is a critical absence of computational, statistical, or bioinformatics expertise. Such expertise is particularly important for a grant such as this, which generates many different orthogonal data types and would best be analyzed in a systems biology context.
- The application should be revised to include appropriate computational biology, and submitted to another (i.e., more basic biology) funding mechanism either at CIRM or elsewhere.
- Better assessment of mechanism of damage, but not a unique or innovative approach.
- Lack of substantiated target.
- Open-ended exploration without obvious route forward.
- The chance of a small molecule being developed from this proposal is fairly small.

DISCOVERY

Application #	DISC2-09501
Title (as written by the applicant)	Micro-scale Energy and Chemical Systems (MECS)-based iPSC-Bioartificial Liver device.
Research Objective (as written by the applicant)	Micro-Scale Energy and Chemical Systems-based technology applied to a Bioartificial liver device using stem cell-derived hepatocytes for liver function support.
Impact (as written by the applicant)	The MECS-BAL design of microfluidic channels and semi-permeable membrane allows for smooth and uniform flow and adherence of cells admitting for maximal mass coverage in support of failing liver.
Major Proposed Activities (as written by the applicant)	• Differentiation of iPSC-stem cells into functional liver cells (hepatocytes) and the ability to freeze and store healthy and sustainable cells that are viable. • Assessment of the differentiated iPSC- liver cells in the single layer MECS-BAL device in terms of function and cell health. • Engineering and assembling a full scale multi-layered MECS-BAL device. • Measuring cell health and functionality of the iPSC-derived liver cells in the full scale MECS-BAL. • Testing the ability of the full scale MECS-BAL for the removal of toxic metabolites from blood with high bilirubin content. • Utilizing a rat model where the rat liver is removed and the MECS-BAL device is connected to prolong the survival of the animal.
Statement of Benefit to California (as written by the applicant)	In California, acute and chronic liver disease is one of the leading causes of over 4000 deaths. Alternative approaches to liver organ transplantation such as the bioartifical liver support systems can improve survival rates. The MECS technology based BAL uses unique microfluidic chambers along with the utilization of iPSC-hepatocytes. Development and clinical translation of this innovative device by academic and industry partnership would help with newer job creation and benefit the economy.
Funds Requested	$798,800
GWG Recommendation	***Tier 2: Not recommended for funding***

Scoring Data

Final Score: 75

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

Mean	75
Median	75
Standard Deviation	4
Highest	80
Lowest	70
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.

DISCOVERY

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

- Significant unmet need; very few advances in this field over the past 10 years.
- Advances in acute liver failure with this device could provide significant insights in the construct of a bioartificial liver.
- This is a stepping stone technology to help patients survive acute liver failure and to eventually create a matrix for a transplantable artificial liver.
- Appealing application: It is logical to populate the MECS-BAL device with hepatocytes derived from human stem cells. This will test their efficacy in short term acute functions. Presumably, the progenitor cells that give rise to the best hepatocytes for the MECS-BAL device will also be the best candidates for stem cell transplants.
- IPSC provide advantage to current approaches.

Concerns

- The design of the microfluidic device is not very innovative and may have issues of long-term viability of cells and issues about scalability and translatability.
- The engineering component of the proposal is weak and not well-thought out.
- The microfluidic device is not state of the art; long narrow flow chambers are not optimal.
- Microfluidics are outdated; collaboration with more advanced expert in microfluidics is necessary to move this proposal forward as present approaches appear to not be feasible.
- The investigators need to team up with a bioengineer with expertise in microfluidics given that the main critique of this proposal is the weakness of the bioengineering part.
- While the cells are a strength of the proposal the integration with the microfluidics is weak.
- Scalability of the microfluidic system to clinical scale is not easy.
- It is not clear if the cells will thrive in these long arrays of parallel microfluidic channels. Seeding of the cells, preventing clogging, fouling and other challenges will be major issues in making this process work.
- Materials of device are not clear.
- This project needs a material science collaborator.
- Device may be used for in vitro testing but not for saving lives.
- Preliminary data with HEK cells, which are very robust, is not relevant.

Additional Comments

- Advise to team up with experts in microfluidic devices.

DISCOVERY

Application #	DISC2-09505
Title (as written by the applicant)	Human Heart-on-a-Chip for Disease Modeling and Developing New Strategies to Treat Cardiac Diseases
Research Objective (as written by the applicant)	This proposal will develop patient specific 'heart-on-a-chip' diagnostics that will have a significant impact on the early screening of drugs used to manage hypertrophic cardiomyopathy.
Impact (as written by the applicant)	Patient specific 'heart-on-a-chip' diagnostics will significantly reduce the cost of bringing a new drug candidate to market while improving efficacy.
Major Proposed Activities (as written by the applicant)	• To develop patient specific 'heart-on-a-chip' diagnostics for drug discovery. • To validate the 'heart-on-a-chip' diagnostic to predict responses to clinical medicines used to manage hypertrophic cardiomyopathy. • To develop a Target Product Profile for the 'heart-on-a-chip' diagnostic. • To develop a manufacturing plan for the 'heart-on-a-chip' diagnostic.
Statement of Benefit to California (as written by the applicant)	One in 500 Californians suffer from hypertrophic cardiomyopathy (HCM), a leading cause of sudden cardiac death in young adults. There are no drugs that target specific disease alleles of HCM. We have developed patient specific 'heart-on-a-chip' diagnostics that will have a significant impact on the development of drugs used to manage hypertrophic cardiomyopathy. If successful, we can reduce the cost and time needed to bring new drugs to market, thereby improving the lives of many Californians.
Funds Requested	$1,096,843
GWG Recommendation	***Tier 2: Not recommended for funding***

Scoring Data

Final Score: 75

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

Mean	78
Median	75
Standard Deviation	4
Highest	85
Lowest	75
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?	6	6	3
Is the rationale sound?	1	9	5
Is the proposal well planned and designed?	1	6	8

DISCOVERY

Is the proposal feasible?	5	5	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

- Area of significant need for drug discovery.
- High relevance to human disease modeling.
- The established tissue chip is a strength.
- Elegant technology.
- Strong cardiac on a chip preliminary data.

Concerns

- The proposal would be improved if the cellular phenotypes could be correlated with patient phenotypes.
- The proposed approach for FDA approval appears premature given the limitations of the model and the lack of correlation with patient phenotypes.
- Lack of evidence that patient-derived iPSCs show similar phenotype as the HCM.
- Genetics may be diverse to generalize/benchmark the findings to the disease model.
- No verification proposed against other in vitro and in vivo systems.

DISCOVERY

Application #	DISC2-09510
Title (as written by the applicant)	Stem cell-derived exosomes to ameliorate radiation-induced cognitive dysfunction
Research Objective (as written by the applicant)	These preclinical studies will discover the best stem cell derived exosome (nanoscale vesicle) based candidate to treat adverse effects of brain cancer therapy on learning and memory.
Impact (as written by the applicant)	To avoid confounders of stem cells (tumors, immunorejection) we will develop a novel strategy, stem cell-derived exosomes, to mitigate the debilitating effects of cancer therapy on learning & memory.
Major Proposed Activities (as written by the applicant)	• Milestone 1: Establish the baseline effect of brain cancer therapy (chemo- and radiation therapy) on cognition using a series of behavioral tests specific to memory and learning centers of the brain. • Milestone 2: Demonstrate the effectiveness of stem cell-derived exosome transplantation to improve cognition in animals receiving chemo- and radiation therapy. • Milestone 3: Determine the ability of exosome transplantation to protect against the adverse effects of cancer therapy on neuronal structure—a determinant of learning and memory. • Milestone 4: Determine the ability of exosome transplantation to improve neuronal function and reduce inflammation — typically impacted by cancer therapy and that contribute to memory impairments. • Milestone 5: Determine early indicators of safety for stem cell-derived exosome transplantation by evaluating tumor formation. • Milestone 6: Determine the molecular contents of exosomes that promote functional recovery of the brain and improve cognition after cancer therapy.
Statement of Benefit to California (as written by the applicant)	In California, nearly 105,000 patients diagnosed with cancer will be alive in 5 years and more than 1.4 million have a history of cancer. Importantly, cancer survivors suffer from severe cognitive impairments that adversely impact quality of life (learning, memory, attention, multi-tasking, planning). Few if any effective treatments exist for this unmet medical need. Our study develops a promising stem cell based therapy to treat the adverse effects of cancer treatment on the brain.
Funds Requested	$1,398,793
GWG Recommendation	***Tier 2: Not recommended for funding***

Scoring Data

Final Score: 75

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

Mean	76
Median	75
Standard Deviation	5
Highest	84
Lowest	70
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

DISCOVERY

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

Reviewer Comments

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

Strengths

- The phenomenon of phenotypic improvement with exosome therapy is worth following up.
- Exciting, innovative concept.
- Excellent preliminary data on restoring cognition and reduced neural inflammation.
- Good proof of principle data has been generated. The applicant demonstrated that exosomes secreted by H9 ESC derived neural stem cells can be implanted into irradiated brains and effectively protect against neural inflammation and restore cognition.
- Evaluating cognitive decline in the context of a combined radiation and chemotherapy treatment is a strength.
- Outstanding assays for behavioral and anatomical assessment.

Concerns

- Irradiation in the context of glioblastoma might be very localized and restricted to the region of resection. This region might not involve the hippocampus. The proposal is thus very limited in its broader interpretation of cognitive impairment in patients treated for brain tumors.
- A key issue is that more biological and mechanistic understanding is needed, as well as understanding what is in these exosomes.
- Weakness in aim 3. There is a need for more mechanistic knowledge of exosomes.
- No feasible strategy for discovering the active principle.
- The proposed studies need to assess in the presence of a tumor burden as well.
- All animal experiments that involve radiation and chemotherapy are conducted in the absence of tumor burden. It is thus possible that the tumor itself contributes to neuronal defects that will not be modeled in the proposed experiments.
- Proof of concept in an animal model leaves a long way to go to get to a human therapeutic, and it is not clear that the animal model is appropriate to relevant human patients to consider this as addressing a major unmet need.
- No justification for focusing cargo investigation only on miRNA.
- A plan for better characterization of the cargo and its specific effects is needed.

DISCOVERY

Application #	DISC2-09526
Title (as written by the applicant)	GENE EDITING FOR FOXP3 IN HUMAN HSC
Research Objective (as written by the applicant)	CRISPR/Cas9 mediated FOXP3 gene editing in patient-derived hematopoietic stem cells as a cure for IPEX syndrome
Impact (as written by the applicant)	FOXP3 mutation in IPEX syndrome leads to immune system dysregulation. Allogeneic HSCT, the only available treatment, has very poor outcomes including GvHD and low immune reconstitution.
Major Proposed Activities (as written by the applicant)	• Demonstrate specificity of targeted insertion of FOXP3 cDNA – ΔNGFR cassette in HD HSCs as assessed by deltaNGFr expression and correct genome integration of the expression cassette. • Demonstrate that edited HD HSCs maintain their proliferative and differentiation potential in vitro using liquid culture, colony forming cell (CFC) and T cell differentiation assay. • Reconstitution of immunodeficient (NSG) mice using gene edited human healthy donor HSCs and demonstration of Teff and Treg in vivo development. • Obtain successful gene editing in IPEX patient HSCs and hu-mouse reconstitution with FOXP3 gene edited HSCs. • Demonstrate in vivo efficacy by amelioration of IPEX-like phenotypes in hu-mice engrafted with gene edited IPEX HSCs, as compared to those injected with not edited.
Statement of Benefit to California (as written by the applicant)	FOXP3 mutation causes dysregulation of Treg and Teff cells leading to immune dysregulation and IPEX syndrome. Using CRISPR/Cas9 gene editing, we will insert a wild type copy of the FOXP3 gene into patient-derived HSCs, enabling pre-clinical proof of concept data for clinical trials that could reduce IPEX patient pathologies. This work will the first-in-man demonstration of the curative potential of edited HSCs and will help maintain California's lead position in Stem Cell research and cure.
Funds Requested	$1,100,568
GWG Recommendation	***Tier 1: Recommended for funding***

Scoring Data

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.

Mean	93
Median	95
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.

DISCOVERY

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	14	0	1
Is the rationale sound?	15	0	0
Is the proposal well planned and designed?	14	1	0
Is the proposal feasible?	14	1	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

- IPEX, a monogenic immune disease with limited therapeutic options, is an ideal candidate for a targeted gene therapy approach.
- This proposal will conduct the preclinical studies required for the development of a cure for IPEX patients using a highly efficient and excellent genome editing approach to repair autologous HSCs.
- The success of this work will be seminal in the subsequent adoption of this approach toward targeted gene repair for treatment of other blood monogenic diseases.
- The proposal has a chance of providing an example of the curative potential of stem cells.
- Applicants have HSCs of 3 IPEX patients and Teff cells and expanded Treg cells from 14 more IPEX patients.
- The proposal presented convincing preliminary data.
- Great investigative team with good expertise in gene editing.
- The proposed milestones are appropriate.

Concerns

- IPEX is a fairly rare disease, so the broad impact is muted.
- There is no plan for looking at off target effects of gene editing technology.

Additional Comments

- The proposal does a good job of addressing concerns from the previous review.

DISCOVERY

Application #	DISC2-09536
Title (as written by the applicant)	The Synthetic Notch Receptor as a Tool for Spatially Targeting Stem Cell Differentiation and Regeneration
Research Objective (as written by the applicant)	This proposal will enable stem cells to autonomously detect features of a niche and respond with a coordinated regenerative program, even in the absence of cues normally required for cell-based repair
Impact (as written by the applicant)	The ability to precisely govern long-term behavior of transplanted stem cells without compromising cellular decision-making processes is absent from existing regenerative medicine strategies.
Major Proposed Activities (as written by the applicant)	• Demonstrate that the synthetic receptor platform functions in induced pluripotent stem cells, mesenchymal stem cells, hematopoietic stem cells, and neural progenitor cells. • Show that the synthetic platform can trigger specific stem cell activities, such as differentiation and migration, to coordinate tissue regeneration and repair in a spatially controlled manner. • Show that effector cells engineered to inducibly express chemokines in response to spatial cues can be used to direct stem and progenitor cell migration in transwell assays. • Show that effector cells can inducibly express anti-inflammatory factors to orchestrate/supplement regenerative behaviors of endogenous cells in response to features of a microenvironment. • Build cell-instructive, synthetic receptor-interfacing biomaterials to spatially guide stem cell behaviors by functionalizing polyethylene glycol-based hydrogels to incorporate cognate ligands.
Statement of Benefit to California (as written by the applicant)	Roughly half of all adults in the U.S. are afflicted by one or more chronic health conditions. The California Department of Public Health estimates that only four of the various classes of chronic diseases afflict 23 million Californians and drive an economic burden that exceeds $74.2 trillion. Here, we propose to develop a guidance system for stem cell-based therapies that solves the unmet need of precisely engineering behaviors of transplanted cells for combating such diseases.
Funds Requested	$1,113,000
GWG Recommendation	***Tier 2: Not recommended for funding***

Scoring Data

Final Score: --

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

Mean	--
Median	--
Standard Deviation	--
Highest	--
Lowest	--
Count	15
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?	4	8	3
Is the rationale sound?	0	9	6
Is the proposal well planned and designed?	3	7	5
Is the proposal feasible?	1	9	5

Reviewer Comments

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

Strengths

- The idea is novel and the proposal is well-written and designed.

Concerns

- Emphasis on the product as a tool would be helpful.
- As presented, the application to stem cells is not clear and may ultimately be limited.
- Preliminary data indicating that this system can affect stem cell function is weak.
- Specifics regarding stem cell type, transcription factor and outcomes would also be helpful.
- What is the in vivo response to biomaterials decorated with synNotch ligands in PEG hydrogels - will they be tolerated, and for how long?
- The notion that this can be used to recapitulate the stem cell niche is a weakness of the proposal, since the niche cues are generally very poorly understood.
- SynNotch receptors may be fine for cell homing to create a favorable regenerative microenvironment but it seems far-fetched to propose these "stem" cells would then produce trophic or modulatory secreted factors, which would then instruct a stem cell niche. One might need several such factors all stimulating interdependent pathways.
- Pilot studies will explore inducing chemokine production, which can in turn be used to recruit stem or progenitor cells that express the cognate chemokine receptor.
  The concern is that inflammation can drive cancer.

DISCOVERY

Application #	DISC2-09542
Title (as written by the applicant)	Multipotent Cardiovascular Progenitor Regeneration of the Myocardium after MI
Research Objective (as written by the applicant)	We developed new technology to prepare large numbers of cardiac progenitor cells from patient iPSCs. We propose to evaluate injection of these cells as a therapy for myocardial infarction.
Impact (as written by the applicant)	Heart failure resulting from myocardial infarction is responsible for 13% of human mortality (WHO statistic). This proposed therapy is to restore the loss of heart cells that lead to heart failure.
Major Proposed Activities (as written by the applicant)	• Perform cell labeling, biobanking and in vitro characterization, including quality control of batches for subsequent activities. • Phase 1: Deliver the progenitor cells (MCPs) into pig hearts after infarction/reperfusion. Use 19F MRI imaging at 24 hours to measure retention and distribution. • Phase 2: Using the conditions determined in Phase 1, monitor animals for 3 months to assess safety & efficacy for improving heart function & survival. Histology at termination to assess regeneration.
Statement of Benefit to California (as written by the applicant)	Heart disease accounts for 25% of deaths in California, making it the #1 cause of death (2014, American Heart Association). Over 3% of Californians have had a heart attack, but with 60% obesity this number will likely increase. The research investigates a curative therapy based on cell transplantation of bonafide cardiac progenitors. Benefits likely to accrue therefore are 1) improved health of our population, and 2) stimulation of biotechnology to produce, market and deliver the therapeutic.
Funds Requested	$1,399,839
GWG Recommendation	***Tier 1: Recommended for funding***

Scoring Data

Final Score: 85

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

Mean	85
Median	85
Standard Deviation	4
Highest	90
Lowest	80
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	1	3

DISCOVERY

Is the rationale sound?	7	4	3
Is the proposal well planned and designed?	9	1	4
Is the proposal feasible?	6	4	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

- Scientific background is solid and a niche area: a real cardiac progenitor.
- The use of true cardiac progenitors is novel and an important strength of this proposal.
- The cells are an advantage.
- Elegant preliminary data on the cell type was presented using genetically manipulated mice.
- Innovative way of delivering and targeting the cells.
- The use of cell retention assays is a strength of this proposal.
- The applicants have expertise in all critical areas.

Concerns

- Not clear if the proposed cell type has a high likelihood of being successful. More preliminary data would strengthen the proposal.
- No preliminary in vivo data to demonstrate the cells will stay alive after delivery to the heart.
- The approach may not be proper.
- Justification for heart integration and persistence of cells seems limited but appropriate studies are proposed.

DISCOVERY

Application #	DISC2-09559
Title (as written by the applicant)	Thin Film Encapsulation Devices for Human Stem Cell derived Insulin Producing Cells
Research Objective (as written by the applicant)	We propose to develop a macroencapsulation technology, based on flexible nanoporous thin films, to support the long term viability and function of human stem cell derived insulin producing cells.
Impact (as written by the applicant)	Encapsulation devices that maintain function of stem cell derived islets can address challenges with current cell therapy for Type I Diabetics, including islet shortage and life-long immunosuppression
Major Proposed Activities (as written by the applicant)	• Enhance beta cell survival by incorporating cell survival factors (e.g. amino acids) into the internal compartment of macroencapsulation device. • Enhance immunomodulatory effects of the macroencapsulation device by incorporating controlled release of soluble anti-TNFa and IL-1Ra from the device. • Determine differentiation and function of macroencapsulated hESC-derived beta cells in vivo over 3 months. • Evaluate biocompatibility of our immunomodulatory thin film macroencapsulation device by monitoring extent of fibrosis and vascularization in vivo. • Examine immune activation by macroencapsulated hESC-derived beta cells in mice with normal immune system. • Test in vivo functionality of devices with hESC-derived beta cells (Graft survival, blood glucose, and c-peptide production over 3-6 months).
Statement of Benefit to California (as written by the applicant)	Diabetes affects 2.3 million Californians with annual healthcare costs of more than $12 billion. An unlimited supply of insulin-producing cells may be produced from stem cells for treating diabetes, but the need for immunosuppression limits the use of this therapy. We will develop a macroencapsulation device that protects these cells from the immune system and enhances long term cell function. Success in this effort may alleviate diabetes-associated disease and financial burden in California.
Funds Requested	$1,092,063
GWG Recommendation	***Tier 1: Recommended for funding***

Scoring Data

Final Score: 87

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

Mean	87
Median	87
Standard Deviation	4
Highest	90
Lowest	80
Count	15
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	13
Tier 2 (1-84): Not recommended for funding	2

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?	13	0	2
Is the proposal well planned and designed?	11	0	4
Is the proposal feasible?	9	3	3

Reviewer Comments

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

Strengths

- Rationale is based on solid justification that future treatments of Type 1 diabetes can be achieved by transplantation of macroencapsulated hESC derived insulin producing cells in the device that provides both alloimmune and autoimmune protection while supporting viability and function.
- Three Co-PIs, an immunologist, stem cell biologist and bioengineer, together provide unique expertise and qualifications required for the success of this application.
- The device design, incorporating Region A with peptides and region B with perimeter immunosuppression, is paradigm changing.
- The approach of hypoxic preconditioning is novel to assist islet survival.
- Three models of transplantation, allogeneic, xenogeneic and humanized, add significant rigor to the experimental design.
- Approach to characterize host T cell responses to islets and SCIPCs in devices for all transplant configurations proposed are very impressive and probably the strongest and most novel component of the proposal.
- Very strong Aim 3 with well-thought-out immunological approaches to understanding the immune responses to the combination device that are relevant to the human disease.

Concerns

- Little experimental details on differentiation of hESCs to insulin-producing cells (SCIPCs) is provided except for a brief mention in the preliminary results.
- Strong preliminary data on single components of the device but less strong on the functionality of the combination product in the SC site.
- Minor weaknesses on approach for optimizing the device and approach for stem cell differentiation.
- Data providing evidence that SCIPCs reverse diabetes after transplantation in diabetic immunodeficient mice are shown but poorly-described so it is not clear whether the cells can reverse diabetes right after implantation or if they require an 'adaptation period' (before making the recipient mice diabetic by STZ treatment).
- Functional data showing that insulin-secreting islets or SCIPCs in the devices can reverse diabetes and maintain long-term euglycemia are not provided. This reviewer questions whether encapsulating the insulin-secreting cell products in the devices would allow physiological glucose-stimulated insulin secretion.
- Thin film preserves survival of allogeneic MIN6 cells up to 30 days after transplant. Data providing evidence that cells maintain their functionality in addition to their viability during long-term implantation in the devices are not provided. Data supporting long-term survival (>30 days) are not provided.
- The rationale for protecting the cells from nutrient deprivation by supplementation with amino acids and from the deleterious effects of cytotoxic cytokines (especially since the cytokines cannot diffuse through the film) is not provided.
- Rapamycin (hydrophobic drug) can be incorporated in the film and released with a zero-order release kinetic. PDL1 incorporated in the film can inhibit T cell activation. No data are provided to support the need of delivering immunosuppressive drugs locally in the device. Some of these drugs may compromise revascularization so they may be deleterious to function of device.
- How the device will be modified to get the "best configuration to achieve stable sustained release of amino acids" and what "best" means in terms of measurable outcomes is not specified.

- A schematic of the functionalized device with hydrogel-releasing components would have benefitted understanding of the proposed modifications to the base device presented in the preliminary data.

DISCOVERY

Application #	DISC2-09565
Title (as written by the applicant)	Preclinical development of human hepatocyte progenitor cells for cell therapy
Research Objective (as written by the applicant)	Determine if human hepatocyte progenitor cells, which exist in the normal adult liver, can be maintained and expanded in vitro while maintaining in vivo regenerative capacity.
Impact (as written by the applicant)	Cell transplantation therapy can be an effective alternative treatment for severe liver diseases to liver transplantation, which is severely limited by the lack of available donor organs.
Major Proposed Activities (as written by the applicant)	• Characterize human pericentral hepatocytes and their niche in normal adult human liver • Determine if human pericentral hepatocytes function as progenitor cells in a humanized mouse liver model • Compare the regenerative capacity of human HPCs with mature hepatocytes • Determine the optimum in vitro conditions for maintaining and expanding human HPCs • Examine whether endothelial cells promote in vitro expansion of human HPCs • Assess the liver repopulating capability of long-term culture expanded HPCs
Statement of Benefit to California (as written by the applicant)	Cellular therapy for severe liver disease in the form of hepatocyte transplantation is effective alternative to whole organ transplantation. However, its usage is limited by the severe shortage of healthy primary human hepatocytes. The potential to generate patient-specific sources of hepatocytes from HPCs for cellular therapy would address an immense unmet clinical need.
Funds Requested	$1,655,436
GWG Recommendation	***Tier 1: Recommended for funding***

Scoring Data

Final Score: 90

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

Mean	91
Median	90
Standard Deviation	1
Highest	95
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.

DISCOVERY

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

- Application addresses an unmet clinical need.
- The project has a high likelihood of success.
- This proposal is based on the recent discovery of hepatocyte progenitor cells (HPCs) in the normal adult mouse liver responsible for homeostatic renewal of hepatocytes. The proposed research will translate these mouse findings to the adult human liver.
- The project utilizes well-characterized liver progenitor cells.
- The project design is solid and likely will produce meaningful results that could be used to advance to translation.
- Important product if they succeed - at the very least they will discover new, interesting things about liver biology.
- Excellent preliminary data is presented.

Concerns

- Preliminary data indicates that transplanted hepatocyte progenitor cells will not persist. Note that none remain in the "stem cell" niche immediately adjacent to the central vein. Finding cells that can persist in that niche and contribute to hepatic parenchyma is a real prize - liver restoration would be more permanent.
- Not enough justification or preliminary data is provided as to why a progenitor cell would be long-lived when transplanted.

Additional Comments

- Test restoration of liver function in vivo.
- Test function of cultured hepatocytes differentiated from HPC in artificial liver devices - this may be a good ex vivo assay for the quality of cell batches prior to transplantation.

DISCOVERY

Application #	DISC2-09567
Title (as written by the applicant)	Integration-defective lentiviral vector-mediated gene editing in human pluripotent stem cells
Research Objective (as written by the applicant)	We propose to develop a highly efficient viral vector-based gene editing system to genetically modify human pluripotent stem cells (hPSCs) for their application in research and disease treatment
Impact (as written by the applicant)	The need to efficiently derive genetically modified hPSCs for basic research and disease treatment will be impacted by the development of an efficient and safe gene editing system
Major Proposed Activities (as written by the applicant)	• We will measure gene modification efficiency and potential off-target effect of the proposed strategy by introducing RNAs instead of plasmid DNAs to express the gene editing components in hPSCs • We will evaluate the effect of the amount of the vector input and the vector design on the efficiency of gene modification in hPSCs • We will test a small molecule inhibitor and two adenoviral proteins which modulate the cellular DNA repair mechanism for their effect on vector-mediated gene modification in hPSCs • We will alter the compositions of the viral vector used in gene editing and evaluate the effect of such changes on the efficiency of gene modification in hPSCs • We will modify the plasmid DNA system used in the production of the viral vector for gene modification to increase the biosafety of using viral vector to establish hPSC clones • We will test the optimized gene modification system by inserting a reporter gene into a motor neuron-specific locus in hPSC to allow the isolation of motor neurons derived from hPSC differentiation
Statement of Benefit to California (as written by the applicant)	Stem cell research can benefit the treatment of diseases burdened by high health care costs like Alzheimer's disease or diabetes that may cripple the healthcare system in California and the nation. To perform stem cell-based therapy, it is often necessary to correct the genetic defect in the stem cell genome. The proposed gene editing strategy, if successful, can overcome the low efficiency of gene modification commonly observed with human stem cells and boost the gene correction efficiency.
Funds Requested	$1,042,694
GWG Recommendation	***Tier 2: Not recommended for funding***

Scoring Data

Final Score: 75

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

Mean	71
Median	75
Standard Deviation	5
Highest	75
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

DISCOVERY

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

- Improvements in gene editing in human ESCs are important and expected to accelerate basic studies on gene function, and also for therapeutic applications of ESCs.
- This is a technique proposal and, if successful, extremely important to the field.

Concerns

- It is unlikely that this technology will significantly improve patient care or address a critical bottleneck to the discovery, development or use of stem cell-based therapies.
- The study is not disease-focused.
- Translation is left for other investigators to apply the deliverables from this proposal.
- It is not clear how significant the proposed improvements will be for therapeutics.
- Significance and potential impact of this application on regenerative medicine are moderate.
- What are efficiencies of HDR with this approach at medically relevant, difficult to target loci?

Additional Comments

- The application would benefit if a preclinical translational effort to cure a disease would be included.
- The proposal would improve if the optimization would be performed on a disease relevant variant.
- Collaborations with disease researchers would increase enthusiasm.

DISCOVERY

Application #	DISC2-09569
Title (as written by the applicant)	hNSC-mediated delivery of ApiCCT1 as a candidate therapeutic for Huntington's disease
Research Objective (as written by the applicant)	The therapeutic candidate is a human Neural Stem Cell that secretes a protein, ApiCCT1, that aids in the prevention of disease phenotypes, for application in treatment of Huntington's disease (HD).
Impact (as written by the applicant)	No treatment currently exists that can slow or prevent the unrelenting progression of Huntington's disease, a devastating brain disease, therefore a completely unmet medical need exists.
Major Proposed Activities (as written by the applicant)	• Generation of a Good Manufacturing Practice (GMP) grade lentivirus to deliver ApiCCT1 to stem cells. • Generation of a quality controlled bank of GMP grade human Neural Stem cells (hNSCs) that express a secreted form of the molecular therapeutic (ApiCCT1) and characterization of ApiCCT1 expression. • Test delivery of ApiCCT1 expressing hNSCs to the striatum of Huntington's disease mouse model and determine whether this stem cell candidate can provide neuroprotection. • Manufacture of a GMP grade human embryonic stem cell (hESC) bank with ApiCCT1 integrated into the genome at a safe harbor site. Cells will be characterized and expanded. • Test delivery of hESC-derived hNSCs expressing secreted ApiCCT1 to the striatum of rapidly progressing HD mice and determine whether this stem cell candidate can provide neuroprotection. • Test delivery of hESC-derived hNSCs expressing secreted ApiCCT1 to the striatum of slower progressing HD mice and determine whether this stem cell candidate can provide neuroprotection.
Statement of Benefit to California (as written by the applicant)	The disability, loss of personal freedom and earning potential, and costly institutional care of Huntington's disease (HD) is devastating. Developing a candidate therapeutic for HD will benefit the State through new technologies and intellectual property resulting in possible job creation and revenues in new companies, in addition to the potential for substantial reductions in individual suffering, medical and care-giving costs.
Funds Requested	$1,787,543
GWG Recommendation	***Tier 1: Recommended for funding***

Scoring Data

Final Score: 90

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

Mean	90
Median	90
Standard Deviation	2
Highest	94
Lowest	84
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

DISCOVERY

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	1
Is the rationale sound?	10	2	2
Is the proposal well planned and designed?	13	1	0
Is the proposal feasible?	12	1	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

- This project is focused on integrating the preclinical therapeutic benefit of human stem cell transplantation with the delivery of a therapeutic drug in the context of Huntington disease.
- This proposal is based on two sets of data each reporting a potential for clinical applicability. The first set is presented to show the potential of hNSC transplanted cells into the brains of various HD mouse models to generate some behavioral benefits with a positive impact on host neuronal elements as well. The second set of data demonstrates that the compound ApiCCT1 can be incorporated into cells and target mHtt. This is an interesting and valuable approach and a strength that two methodologies will be used as a combinational therapy.
- The preliminary data is strong and warrants further pre-clinical work on the combinational approach proposed.
- The application builds logically on previous data and is potentially highly relevant and exciting.
- Laser-like focus on moving the approach forward with cGMP.
- Clever strategy for enhancing efficacy by combination therapy.

Concerns

- There are some concerns with potential off target effects, ensuring sustained delivery of the ApiCCT, analysis of in vivo ApiCCT levels and efficacy of cell survival after transplantation.
- Out of 7 trials with stem cells only one has shown very marginal gains which were short-lived. Lack of persistence of cells appears to be a major hurdle.
- Cell survival following transplantation is very low in HD due to the severe pathology in which cells are placed. Unclear how this will be bypassed/avoided with hNSC.
- Most of the preliminary data shown was derived from animals treated before the pathology developed. This does not equate to human presentation suggesting this model may not be so relevant.
- It is unclear how the sustained delivery of ApiCCT1, which seems necessary to attain behavioral amelioration in mice (preliminary data provided), would be ensured in patients.
- There are concerns about off-target effects of sApiCTT1.
- Mechanisms of action are unclear.
- Applicants claim that tumor growth analysis were negative in preliminary data. However preliminary data figures clearly show that Ki67, a marker of proliferating cells, is expressed by hNSC post-transplantation.
- All histology provided in preliminary data is suboptimal. For example, results of ApiCCT1 delivery on mHtt aggregates is very interesting but the histology is suboptimal as one can barely distinguish the inclusions within the cell body.

Additional Comments

- It would be good to focus on the mechanisms of action to understand how to optimally use this approach or develop better approaches along these lines.

DISCOVERY

Application #	DISC2-09585
Title (as written by the applicant)	Treating Duchenne muscular dystrophy with Cas9 based gene editing of satellite cells.
Research Objective (as written by the applicant)	We propose to develop a new delivery vehicle termed CRISPR-Gold, which is designed to deliver Cas9 protein, gRNA and donor DNA into satellite cells in vivo, and treat Duchenne muscular dystrophy.
Impact (as written by the applicant)	CRISPR-Gold is the first non-viral therapeutic that can correct dystrophin mutations back to their wild type sequence and has the potential to have a transformative effect on the treatment of DMD.
Major Proposed Activities (as written by the applicant)	• Enhance the homology directed repair efficiency of CRISPR-Gold therapy in vivo by co-administration with FDA approved muscle stimulating agents that activate satellite cells for myogenesis. • Develop a novel CRISPR-nanoparticle drug delivery vehicle that has a biodegradable core instead of a gold core, which has a gene editing efficiency equivalent to or better than CRISPR-Gold. • Develop new CRISPR-Gold and CRISPR-nanoparticle formulations that can be produced on a large scale, have low toxicity, and have low batch to batch variation. • Identify eligible DMD patients for a first CRISPR-Gold clinical trial and develop personalized CRISPR Gold formulations for them, which can correct patient specific dystrophin mutations.
Statement of Benefit to California (as written by the applicant)	Duchenne muscular dystrophy(DMD) is a lethal genetic disease of children which has no treatment or cure till date. Approximately 1 in 2400 boys have this disease and die before age 30. This deadly disease has also affected citizens of California. The proposed research will be a huge step towards finding a biocompatible, non-immunogenic, and efficient cure for DMD by gene editing of the muscle stem cells and could potentially be used in a California clinic in a few years.
Funds Requested	$2,117,166
GWG Recommendation	***Tier 2: Not recommended for funding***

Scoring Data

Final Score: --

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

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

DISCOVERY

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	6	6	3
Is the rationale sound?	0	12	3
Is the proposal well planned and designed?	1	12	2
Is the proposal feasible?	0	11	4

Reviewer Comments

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

Strengths

- This proposal will address an unmet clinical need by developing a gene therapy approach for DMD.

Concerns

- This is more a basic science proposal that is working out the best way to deliver CRISPR repair of DMD, than an approach to directly treat humans.
- Delivery of CRISPR-Gold to enough tissues and achieving gene correction in enough cells to aid DMD patients is critical to the success of this or any gene-correction therapy. It is not clear if the current proposal will solve these issues. However, the PI is well-aware of these problems.
- Proposal deals mostly with improvements in in vivo delivery of CRISPR/Cas9 system to muscles. It is unclear how the proposal will increase HDR.
- Is it unclear whether the approach will specifically target satellite cells.
- The proposal lacks preliminary data to demonstrate that satellite cells are targeted with this strategy.
- Most of the proposed experiments are in the mouse model with little extension to patient iPSCs.
- The need for agents to stimulate DMD patient's satellite cells to divide is problematic.
- Potential pitfalls are pointed out for each section, however they may not solve potential issues. For example, if 20% efficiency is not obtained other muscle regeneration approaches will be used (exercise). Exercise may allow the team to approach the 5% CTX efficiency but it is not clear how this will decrease the number of injections needed.
- The repair rate needed for improvement in patients is unclear. The single mouse experiment suggested that, at least in one test, 0.8% repair in two muscle results in some benefit. A discussion of how this relates to humans would be useful.

DISCOVERY

Application #	DISC2-09592
Title (as written by the applicant)	Real-time monitoring of stem cell differentiation for quality assurance in regenerative medicine applications
Research Objective (as written by the applicant)	Real time cell imaging tool with novel software analysis that screens for contaminant cells during manufacturing of stem cell therapies to assure safety and quality of the final treatment cell dose.
Impact (as written by the applicant)	This tool does not harm the cells and can track the entire stem cell population during manufacturing to ensure safety. It can also be used in research to examine critical events in stem cell biology
Major Proposed Activities (as written by the applicant)	• Build the tool prototype and optimize software algorithms to detect pluripotent stem cell contaminants and unwanted cell byproducts during stem cell differentiation • Test the prototype and software using cell mixtures of know pluripotent stem cell contaminants and unwanted cell byproducts from stem cell differentiation process • Optimize laser dissection tool to support extraction of unwanted cell subpopulations during stem cell differentiation. This is to allow genetic testing of the unwanted cells to correlate with tool • Reproducibility testing using established protocols for pluripotent stem cell differentiation to mesenchymal and neuronal cells • Correlate software detection results with in vivo tumor formation by harvesting the unwanted cells and transplanting them into immune deficient rodents • Intellectual property filing and draft marketing strategies and plans with industry
Statement of Benefit to California (as written by the applicant)	A critical bottleneck in bringing stem cell therapy to clinical applications is the concern for tumor formation after transplantation. This may be due to stem cell impurities or formation of cancer cells during manufacturing. Our tool can detect these unwanted cells during the manufacturing process. Ultimately, this tool can be used for quality assurance of all stem cell therapies to predict safety and effectiveness. This tool could help Californians receive safe and effective treatments.
Funds Requested	$1,100,568
GWG Recommendation	***Tier 2: Not recommended for funding***

Scoring Data

Final Score: 80

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

Mean	79
Median	80
Standard Deviation	6
Highest	89
Lowest	65
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?	7	4	4
Is the rationale sound?	5	5	5
Is the proposal well planned and designed?	5	2	8
Is the proposal feasible?	4	3	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 proposal addresses an important topic in development of stem cell therapies.
- Micro-dissection offers functional characterization.
- Large scaling based only on one algorithm. Good approach to address an important problem.

Concerns

- Even if successful this application may not provide a great enough impact to merit funding in a competitive environment.
- The proposal is too vague in its design.
- This proposal lacks detail around proposed improvement of the algorithm.
- The characteristics of mathematical simulation are not universal for all cell types.
- Scale-up for application to other cell types seems low since different cell types have different alignments.
- Scale-up for laser micro dissection is incredibly labor intensive. Would need explanation for how to scale-up with this way of decontamination.
- No positive controls to show how to identify contaminants in a specific cell line.
- Need more preliminary evidence that there is enough information content in the measured parameters for an algorithm to work with an adequate ROC.
- Need to avoid or explain jargon. At least one reviewer was unclear of the definition of "texture analysis" - thought maybe it referred to fluffy cell walls.

Additional Comments

- The applicant should find an expert in stem cells and their differentiation, pick a disease and apply this for a specific disease to show efficacy and then proceed with universality or additional applications, i.e. neural or cardiac or islets.
- Mathematical model could incorporate machine-based learning technique to allow for input of multiple cell types- contact guidance, polarity and alignment not sufficient.
- This reviewer would like to see more discussion of alternative algorithmic approaches: for example, how the proposed algorithm compares to a neural net or other machine learning approaches.

DISCOVERY

Application #	DISC2-09596
Title (as written by the applicant)	Direct Cardiac Reprogramming for Regenerative Medicine
Research Objective (as written by the applicant)	To develop a gene therapy product to deliver cardiac reprogramming factors into the heart for regeneration of new heart muscle.
Impact (as written by the applicant)	The proposed candidate would regenerate heart muscle for the 23 million adult and pediatric patients with heart failure, for whom there are currently no disease-modifying therapeutic approaches.
Major Proposed Activities (as written by the applicant)	• Successful conversion of support cells in the heart into new muscle in mice using two viral vectors for gene delivery. • Successful conversion of support cells in the heart into new muscle in pigs using two viral vectors after cardiac injury. • Discovery to allow use of a single viral vector as the therapeutic product for converting human cardiac support cells into cardiac muscle-like cells. • Successful conversion of support cells in the mouse heart into new muscle using a single viral vector for gene delivery. • Successful conversion of support cells in the pig heart into new muscle using a single viral vector for gene delivery. • Establish safety profile of therapeutic for in vivo cardiac reprogramming in the pig model.
Statement of Benefit to California (as written by the applicant)	The proposed research will benefit California by promoting a potential novel therapy for the estimated 500,000 Californians who suffer from heart failure, including adults and children. Furthermore, California will benefit from reduced medical costs if this therapy is successful, as complications related to heart failure are the number one cause of hospitalizations. Finally, California will benefit from the development of this technology as part of the growing biotechnology economy.
Funds Requested	$2,400,048
GWG Recommendation	***Tier 1: Recommended for funding***

Scoring Data

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.

Mean	88
Median	88
Standard Deviation	4
Highest	95
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.

DISCOVERY

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	12	1	1
Is the rationale sound?	11	0	3
Is the proposal well planned and designed?	13	0	1
Is the proposal feasible?	13	1	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 project has a high likelihood of developing a new treatment approach.
- Strong rationale and approach to solve the problem.
- Strong preliminary data.
- Excellent study design.
- A significant strength of this proposal is the additional translational steps that are taken including small molecules.
- The data that involve generation of a new AAV is a significant strength of this proposal.
- The investigator and his track record in the field are a strength.

Concerns

- The off-target effects of the vectors on cardiac cells are unclear.
- There are concerns about translatability, such as what the target cells are for reprogramming in vivo, and given that 25% of the cells targeted are cardiomyocytes what happens to these cells.

DISCOVERY

Application #	DISC2-09601
Title (as written by the applicant)	Stem cell enabled development of a therapeutic candidate against Huntington's Disease
Research Objective (as written by the applicant)	Identify a small molecule drug candidate that prevents the accumulation of neurotoxic proteins and supports the survival of neuronal cells in Huntington's Disease
Impact (as written by the applicant)	We will deliver first-in-class compounds for the development of therapeutic agents against a broad spectrum of currently untreatable neurodegenerative diseases.
Major Proposed Activities (as written by the applicant)	• Small molecule screening campaign to identify chemical matter that can prevent the accumulation of mutant Huntingtin protein • Optimize screening hits to obtain specific cellular activity in neuronal derivatives of hESCs • Establish compound activity in cell and animal models of Huntington's Disease, including hESC- and patient-derived iPSC-based systems expressing various forms of mutant Huntingtin protein.
Statement of Benefit to California (as written by the applicant)	Neurodegenerative diseases affect a growing number of patients in California and beyond. Currently, there is not a single treatment option that slows, halts, or reverse the progression of these deadly diseases. California has invested heavily in centers that investigate the molecular mechanisms of neurodegeneration. The proposed work will extend this investment to push forward first-in-class compounds as therapeutic options against neurodegenerative diseases.
Funds Requested	$1,130,616
GWG Recommendation	***Tier 2: Not Recommended for funding***

Scoring Data

Final Score: 70

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

Mean	73
Median	70
Standard Deviation	6
Highest	85
Lowest	60
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?	6	5	4
Is the rationale sound?	2	9	4

DISCOVERY

Is the proposal well planned and designed?	4	6	5
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

- High-risk but potentially high-gain project. Strongly depends on successful initial screening.
- Extremely elegant biochemical analysis and small molecule screen activities are proposed.
- PI is a major contributor to the field of proteasomal degradation of protein.

Concerns

- No evidence that small molecules can enhance UBQLN2.
- There are concerns about off-target effects and the proposal gives no consideration to these effects.
- Each section has an alternative approach section, but the sections do not offer alternative approaches.
- It is not clear how the small molecule will be administered to the HD mice.
- Not clear if candidates will be specific to HD.
- It is unclear if increased degradation of all protein aggregates will have adverse effects since the system is likely not specific to HD.

DISCOVERY

Application #	DISC2-09602
Title (as written by the applicant)	Recovery of brain function by mitochondria transfer from stem cells to injured neurons
Research Objective (as written by the applicant)	Impaired energy metabolism is a potential target of traumatic brain injury therapy which could be accomplished by transferring mitochondria and trophic factors from stem cells to damaged neurons
Impact (as written by the applicant)	Traumatic brain injury as well as other neurological conditions with mitochondrial dysfunction (e.g., Alzheimer's)
Major Proposed Activities (as written by the applicant)	• Time-dependency of the type and degree of severity of mitochondrial dysfunction (MD) in brain with traumatic brain injury (TBI). This will be accomplished by combining functional and "omics" studies. • The type and degree of severity of MD in TBI is not ascribed solely to the affected area but also to other areas with high glia-to-neurons ratio (mitochondria-derived inflammatory response) • The type and degree of severity of MD in TBI is more drastic in males than females due to the protective effect of estrogen on mitochondria function • Treatment with stem cells increases the transfer of mitochondria and/or trophic factors from stem cells to damaged tissue increasing the energy output. • Co-culture of stem cells with TBI-derived primary neurons allows the release of mitochondria, trophic factors and/or exosomes promoting mitochondrial transfer and biogenesis in neurons • Treatment of TBI-affected rodents with stem cells improves the recovery of brain function and behavior (memory, cognitive)
Statement of Benefit to California (as written by the applicant)	TBI accounts for 1.7 million emergency room visits/year by US citizens representing the world-wide leading cause of morbidity and mortality in individuals <45 y old with ~80,000-90,000 experiencing long-term disability. The most recent TBI surveillance report estimated that of the 12 reporting states, CA (with 75.8/100,000) placed 8th indicating the need for prevention and effective treatments that will minimize the TBI-related debilitating effects in our State.
Funds Requested	$823,700
GWG Recommendation	***Tier 2: Not recommended for funding***

Scoring Data

Final Score: --

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

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

DISCOVERY

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	4
Is the rationale sound?	1	12	2
Is the proposal well planned and designed?	0	12	3
Is the proposal feasible?	1	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

- Limited treatment options are available for traumatic brain injury (TBI) so there is an unmet clinical need.

Concerns

- All reviewers noted that preliminary data section is missing, a serious omission for this grant mechanism.
- The applicant demonstrates under-appreciation of established work in the field.
- The idea of transplanting an astrocyte-committed precursor is potentially attractive, but the field has moved on from thinking of astrocytes as homogeneous populations. Information is needed on what the cells become, both *in vitro* and *in vivo*.
- The applicant is focused on a single cell line in the absence of any evidence that this cell line is better or worse in comparison to outcomes that would be achieved with other cell lines. Without such data, dedication of a single cell line is premature.
- The proposal is unlikely to result in any treatment.
- The proposal lacks any description of human MSC production, transplantation, integration and xeno mitochondrial exchange.
- TBI is a diffuse disease and the applicant is planning a focal therapeutic.
- MSC may not distribute sufficiently *in vivo* to address TBI.
- Biomarkers are limited to brain and therefore unclear how these data be applied noninvasively as biomarkers.
- Experiments demonstrating mitochondrial transfer are missing.

Additional Comments

- Gene expression analysis is not mechanism of action. Gene expression analysis might be useful for determining characteristics of cell lines that offer different degrees of benefit.

DISCOVERY

Application #	DISC2-09610
Title (as written by the applicant)	CRISPR/dCas9 mutant targeting SNCA promoter for downregulation of alpha-synuclein expression as a novel therapeutic approach for Parkinson's disease
Research Objective (as written by the applicant)	Discovery of a novel therapeutic candidate for Parkinson's disease which modifies gene expression using human stem cell-derived neurons to halt the neurodegenerative disease process.
Impact (as written by the applicant)	Stopping the neurodegenerative process of Parkinson's disease is a critical unmet medical need. Our approach is based on novel gene engineering technology that modifies expression of key target genes.
Major Proposed Activities (as written by the applicant)	• Identification and engineering of therapeutic candidates that downregulate expression of test gene in human stem cell-derived neuronal precursor cells. • Measurement of target gene downregulation in human stem cell-derived neuronal precursor cells and neurons with assessment of phenotype rescue. • Testing downregulation of target gene using relevant pre-clinical model containing endogenous gene regulatory regions. • Development of a Target Product Profile for advancement of the therapeutic candidate for CIRM partnering opportunity: translational research projects (TRAN). • Preparation for stage appropriate regulatory meetings for subsequent CIRM pre-clinical application. Develop regulatory strategy with CIRM Clinical Advisory Panel.
Statement of Benefit to California (as written by the applicant)	Estimated 36,000-60,000 people in the State of California are affected with Parkinson's disease which is a neurodegenerative disease that causes a high degree of disability and financial burden for our health care system. This collaborative project will provide substantial benefits and values to the state of California and its citizens by developing new therapeutic candidates for the treatment of Parkinson's disease enabled by stem cell technologies and gene therapy.
Funds Requested	$1,931,589
GWG Recommendation	***Tier 1: Recommended for funding***

Scoring Data

Final Score: 85

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

Mean	87
Median	85
Standard Deviation	7
Highest	100
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	1	3
Is the rationale sound?	8	3	4
Is the proposal well planned and designed?	12	3	0
Is the proposal feasible?	9	3	3

Reviewer Comments

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

Strengths

- Parkinson's disease is the second most common neurodegenerative disorder, affecting more than 5 million people worldwide. No neuroprotective or neuro-restorative therapy exists for treatment of this chronic disorder.
- SNCA is an important potential target, and this novel stem cell therapy might work.
- There is substantial preliminary data indicating that the strategy will be effective in knocking down SNCA levels.
- The revised proposal amply addresses all the concerns raised in the previous review.
- Clear plan for moving forward toward translational use.
- High rationale for this work given that many current trials are focusing on alpha-synuclein.
- Concerns about whether non-specific targeting to non-dopaminergic neurons will be problematic can only be determined by doing the experiment.

Concerns

- The hypothesis that alpha-synuclein regulation in sporadic PD is of pathogenic or therapeutic relevance appears to be largely speculative at this stage. If this hypothesis is wrong, then the value of this approach may be very restricted.
- The CNS is composed of multiple cell types that represent most of the volume and surface area in this tissue. There is a concern about whether the virus will simply be taken up by other cells and what will be the consequences to the patient.
- Specificity of targeting may not be sufficient; some proof should be submitted on specificity of targeting.
- As only a small amount of misfolded alpha-synuclein seems to be sufficient to unleash a cascade of abnormal processing, it is unclear whether the degree of attainable knockdown will be sufficient to change the course of disease.
- As a great deal of damage already is present at the time of diagnosis, it is important to demonstrate that delivery of the proposed therapy in an animal model at a stage when clinical symptoms are well-expressed is therapeutically relevant.

DISCOVERY

Application #	DISC2-09615
Title (as written by the applicant)	Targeted off-the-shelf immunotherapy to treat refractory cancers
Research Objective (as written by the applicant)	This project will use human pluripotent stem cells to produce a standardized, off-the-shelf immunotherapy using novel immune cells that are specifically targeted to cure otherwise lethal cancers.
Impact (as written by the applicant)	Unlike current immunotherapies produced on a patient-specific basis, iPSC-derived immune cells are targeted to tumors with high specificity, no off-target effects and without need for patient matching
Major Proposed Activities (as written by the applicant)	• Produce novel human iPSC-derived natural killer (NK) cells expressing a specifically designed receptor (CAR) to more effectively and efficiently target and kill human ovarian and other cancer cells. • Engineer novel NK cell-specific CAR constructs with NK cell-specific intracellular signaling domains to enhance iPSC-NK cell activation upon recognition of ovarian cancer target cells. • Optimize anti-leukemia activity of iPSC-derived NK cells using defined iPSC-NK cell populations with differing receptor profiles that target specific tumor profiles. • Optimize iPSC-NK cell expansion using systems that can be rapidly translated into clinical cell production. This will ensure we efficiently produce enough targeted iPSC-NK cells for clinical trials.
Statement of Benefit to California (as written by the applicant)	Cancer remains the second leading cause of death in California, the US and worldwide. Despite advances in many areas of cancer treatment including chemotherapy and even immunotherapy, outcomes for relapsed or refractory cancers remain dismal. Here, we will use human iPSCs as the basis to develop a novel targeted cell population that can serve as a universal cellular immunotherapy to better treat and cure cancers for potentially thousands of patients in California each year.
Funds Requested	$2,134,868
GWG Recommendation	***Tier 1: Recommended for funding***

Scoring Data

Final Score: 90

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

Mean	91
Median	90
Standard Deviation	2
Highest	95
Lowest	88
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.

DISCOVERY

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

- Optimal iPSC- derived NK cell product and expansion strategy is expected to translate to a novel targeted, “universal” and “off-the- shelf” cellular therapy to treat thousands of patients with relapsed/refractory cancers that do not have an effective therapeutic option.
- The target is relevant.
- NK cells kill tumors and virally-infected cells in non-HLA-restricted manner.
- iPSC-derived NK cells are >97% NK cells.
- Clearly relevant preliminary data demonstrates feasibility.

Concerns

- Studies to explore all combinations of signal transduction elements of CARs seem ambitious.
- It is unclear why there is no anti-NK cell immune response for the iPSC-derived NK cells.
- The leukemia model of CML/APL are not as relevant as a better AML model.

DISCOVERY

Application #	DISC2-09617
Title (as written by the applicant)	iPS Glial Therapy for White Matter Stroke and Vascular Dementia
Research Objective (as written by the applicant)	The studies will develop an iPS-glial enriched progenitor cell line (iPS-GEPs) for brain repair in white matter stroke.
Impact (as written by the applicant)	This cell line will target tissue repair and recovery in ischemic white disease, a chronically progressive dementing condition with no current therapy.
Major Proposed Activities (as written by the applicant)	• Efficacy. 1) Test efficacy of iPS-GEPs in chronic white matter stroke; 2) Test the efficacy of transplant location; 3) Test the dose response; 4) Test optimum dose and timing in aged mice • Mechanism of Action. 1) Identify in vivo expression profile of iPS-GEPs during period of tissue repair; 2) Correlate behavioral recovery effect with levels of candidate molecular systems in iPS-GEPs • Assay Development. Based on preliminary RNAseq studies of iPS-GEPs: 1) Develop identity assays for iPS-GEPs; 2) Develop purity assays for iPS-GEPs; 2) Develop activity assays for iPS-GEPs • Mechanism of Action. 1) Identify in vivo expression profile of iPS-GEPs during period of tissue repair; 2) Correlate behavioral recovery effect with levels of candidate molecular systems in iPS-GEPs
Statement of Benefit to California (as written by the applicant)	Stroke is the leading cause of adult disability. White matter stroke occurs in the connecting areas of the brain. This entity is up to 30% of all stroke and the second leading cause of dementia. There is no therapy for this disease. White matter stroke damages the specialized cells that support brain connections, glial cells. The proposed studies develop a specifically tailored stem cell therapy for tissue repair in white matter stroke, an induced pluripotent glia cell.
Funds Requested	$2,080,925
GWG Recommendation	***Tier 2: Not recommended for funding***

Scoring Data

Final Score: 80

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

Mean	78
Median	80
Standard Deviation	5
Highest	84
Lowest	69
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.

DISCOVERY

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	9	4	2
Is the rationale sound?	6	6	3
Is the proposal well planned and designed?	1	8	6
Is the proposal feasible?	4	4	7

Reviewer Comments

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

Strengths

- The proposal presents a good rationale by a great team.
- The preliminary data demonstrate behavioral recovery.
- Glial enriched progenitors (GEPs) can migrate widely. It would be good to know if this is co-terminus with the injury.

Concerns

- Weak milestones as written- i.e. no quantification of read-outs. This is not mechanistic as written and is descriptive/correlative.
- There was a consensus that there should be use of more than one iPS cell line.
- The dedication to a single cell line in the absence of any demonstration that this cell line is equally, effective than alternatives is an unjustified assumption.
- There is concern about the lack of attention to the types of astrocytes that the transplanted cells are becoming. For example, if the transplant generated largely astrocytes that expressed markers of glial scar then there would be a concern as to whether this was the best cell type to transplant.
- The plan for mechanistic analysis is not satisfactory. For example, performance of scRNA-seq analysis does not adequately address mechanism of action.
- The idea that gene expression is a meaningful exploration of mechanism of action is not supported, and seems superficial. Such expression studies might become more meaningful if there were multiple cell lines, made in identical ways that had different degrees of efficacy.
- Whether there is an inflammatory response to the cells was not addressed.
- Hard to know if the milestones will be feasible as there is no quantification and little specificity.
- Migration of cells is demonstrated but final differentiation/function may be variable based on batch to batch variability.
- Previously highlighted weaknesses have not been addressed yet.

DISCOVERY

Application #	DISC2-09624
Title (as written by the applicant)	Protein tyrosine phosphatase - sigma inhibitors for hematopoietic regeneration
Research Objective (as written by the applicant)	We propose to develop a lead small molecule inhibitor of PTPσ, a receptor expressed by human blood stem cells, for the purpose of promoting human hematopoietic regeneration.
Impact (as written by the applicant)	Systemic administration of a PTPσ inhibitor can accelerate hematologic recovery in thousands of patients who have received myelosuppressive chemo- or radiotherapy.
Major Proposed Activities (as written by the applicant)	• Generate novel PTPσ inhibitors for functional screening. • Develop and validate a PTPσ inhibition assay to allow direct testing of candidate PTPσ inhibitors in vitro. • Develop and validate a Rac1 activation assay and a PTPσ specificity assay and test all candidate PTPσ inhibitors for these activities. • Determine the in vitro and in vivo hematopoietic regenerative capacity of select PTPσ inhibitors. • Test the efficacy of select PTPσ inhibitors in a model of BM transplantation and against human HSCs in vitro. • Perform initial PK and toxicity studies of PTPσ inhibitors and select a lead compound for clinical development.
Statement of Benefit to California (as written by the applicant)	This research will benefit California in several ways. First, this research provides fundamental new knowledge regarding hematopoietic stem cell biology to the field. Second, we have generated new intellectual property around novel PTPσ inhibitors for which we have filed provisional patent applications with the USPTO. Third, our discoveries will provide the basis for licensure to biotechnology or pharmaceutical companies in California or raise investment from venture capitalists.
Funds Requested	$2,116,708
GWG Recommendation	***Tier 1: Recommended for funding***

Scoring Data

Final Score: 90

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

Mean	90
Median	90
Standard Deviation	3
Highest	95
Lowest	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.

DISCOVERY

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

- There is a need for a drug that can stimulate HSCs; so, if successful, this could be of great impact.
- The applicant has a candidate molecule with strong translational potential.
- The molecule optimization and the chemical modifications proposed are very strong.
- The use of human stem cells is a significant strength of the proposal.
- Excellent product development plan.
- Two assays established for screening efficacy of the proposed 60 compounds.
- Excellent proof of concept in irradiated mice.
- The team has the necessary expertise to carry out the experiments.

Concerns

- The data presented in figure 2 are unclear.
- This reviewer would have preferred to have seen a standard competitive repopulation assay for the activity of PTP sigma deficiency.

DISCOVERY

Application #	DISC2-09627
Title (as written by the applicant)	Neural Stem Cell Delivery of Oncolytic Virus for Targeted Treatment of Ovarian Cancer Metastases
Research Objective (as written by the applicant)	Demonstrate proof-of-concept for use of a clinically relevant tumor-tropic neural stem cell (NSC) platform to selectively deliver an oncolytic virotherapy to ovarian cancer metastases (Stage III).
Impact (as written by the applicant)	This NSC-delivered virotherapy approach will lead to a much needed more effective, less toxic treatment for patients with metastatic ovarian cancer, inducing cell death even in chemoresistant cells.
Major Proposed Activities (as written by the applicant)	• Determine clearance kinetics of CRAd-S-pk7 adenovirus after single and repeat intraperitoneal (IP) injections in immunodeficient and humanized mouse models of human peritoneal ovarian metastases. • Determine oncolytic therapeutic efficacy of repeat IP administrations of CRAd-S-pk7-NSCs +/- cisplatin in NSG mice bearing low ovarian tumor burden by monitoring long-term survival and tumor growth • Determine anti-cancer immune response to repeat IP administrations of CRAd-S-pk7-NSCs +/- cisplatin in humanized mice bearing low ovarian tumor burden by monitoring long-term survival and tumor growth • Determine the most efficacious dose and regimen of IP CRAd-S-pk7-NSCs +/- cisplatin in humanized mice bearing low ovarian tumor burden by monitoring long-term survival and tumor growth. • Determine the anti-cancer immune response to repeat IP administrations of CRAd-S-pk7 +/- cisplatin in humanized mice bearing high ovarian tumor burden by monitoring long-term survival and tumor growth • Complete Data/statistical analysis, summarize results, and finalize figures for presentation and publication. This will provide the foundation for next step translational studies.
Statement of Benefit to California (as written by the applicant)	Ovarian cancer is the most lethal gynecologic malignancy, resulting in 1,500 deaths annually in California. At diagnosis, >70% of patients already have metastases throughout their abdomen, leading to a dismal 34% 5-year survival rate. We anticipate that our stem cell-delivered oncolytic virotherapy will lead to a more effective, less toxic treatment for these patients that will kill even metastatic tumor foci and chemoresistant cells, improving survival of ovarian cancer patients in California.
Funds Requested	$1,757,793
GWG Recommendation	***Tier 2: Not recommended for funding***

Scoring Data

Final Score: --

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

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

DISCOVERY

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?	3	9	3
Is the rationale sound?	0	13	2
Is the proposal well planned and designed?	1	10	4
Is the proposal feasible?	1	11	3

Reviewer Comments

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

Strengths

- The proposed studies are logical for the goals of the project.

Concerns

- Despite progress from prior funding cycles, this approach is not any closer to a therapeutic.
- History of treatment with oncolytic viruses is overall not reliably successful.
- Infusion of neuroepithelial cells for treatment of ovarian cancer presents high variability and low feasibility to deliver adequate therapy for several reasons, including immunogenicity of the cells, variable homing, and persistence of cells for effect.
- The demonstration of therapeutically relevant effects is not convincing. Considering the poor successes of viral oncolytic therapies, there is a need to provide compelling demonstrations of such efficacy.
- Homing of the NSC to the target was not convincing. This needs to be done in an immunocompetent model.
- GBM data on this kind of technology is anecdotal.
- Pitfalls are not thoroughly addressed.
- It is not clear that the NSCs are not immunogenic.

Additional Comments

- Demonstration of viral spread in a malignant tumor model is very important to provide.
- Data regarding homing of NSCs in humans would be extremely helpful.

DISCOVERY

Application #	DISC2-09631
Title (as written by the applicant)	Identification and characterization of the optimal human neural stem cell line (hNSC) for the treatment of traumatic brain injury (TBI).
Research Objective (as written by the applicant)	We propose to discover the optimal human neural stem cell candidate for traumatic brain injury (TBI). 4 hNSC products (2 ES and 2 fetal) will be compared with sham and controls, and then each other.
Impact (as written by the applicant)	Traumatic brain injury (TBI) affects more Americans than brain, breast, colon, lung and prostate cancer combined! There are no approved therapies for TBI, we hope to change that.
Major Proposed Activities (as written by the applicant)	• Obtain 2 GMP grade human ES cell lines. • Expand/sort ESCs to hNSC and produce sufficient quantities to transplant into 20 ATN rats at a dose of 500K per animal. • Test each ES derived hNSC line in an CCI animal model of TBI for efficacy on four different tasks, two for memory and two for emotional changes. • Obtain 2 GMP grade human fetal cell lines. • Expand fetal lines to hNSC and produce sufficient quantities to transplant into 20 ATN rats at a dose of 500K per animal. • Test each human fetal derived hNSC line in an CCI animal model of TBI for efficacy on four different tasks, two for memory and two for emotional changes.
Statement of Benefit to California (as written by the applicant)	1.7 million American's experience a Traumatic Brian Injury (TBI) leading to hospitalization (200,000 Californians), at a cost to society of $76.5 billion each year (~$9.3 billion to California). TBI can result in permanent cognitive and emotional deficits. Transplantation of human neural stem cells (hNSCs) could lead to improvements in learning & memory, or emotion that could significantly change a patient's quality of life and have considerable economic impact to the people of California.
Funds Requested	$1,557,203
GWG Recommendation	***Tier 1: Recommended for funding***

Scoring Data

Final Score: 85

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

Mean	87
Median	85
Standard Deviation	10
Highest	100
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.

DISCOVERY

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	11	0	3
Is the rationale sound?	8	2	4
Is the proposal well planned and designed?	10	2	2
Is the proposal feasible?	9	2	3

Reviewer Comments

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

Strengths

- Traumatic brain injury (TBI) is an increasing and very challenging problem that comes with a high burden for society and there are very few approaches that could be moved forward to the clinic.
- TBI has a major unmet need. It has large population level morbidity and mortality.
- Models of TBI are time-consuming and highly variable and any approach that is suitable to gain insight into the complexity of this disease has an impact on a highly unmet medical need.
- One of the strengths of this approach is that even small reduction in lesion volume could lead to significant improvements and long-term benefit. This makes a stem cell approach particularly suitable for TBI.
- This is an incremental project. Careful work that moves stem cell research on TBI forward. Not necessarily flashy, but essential.
- The applicant has constructed a very thoughtful application that is focused on bringing a stem cell therapy to the clinic.
- This is a beautifully constructed grant that has the right focus and attention to detail to be successful.
- This new application builds on earlier findings which were supported by a CIRM early translational award and provides a logical extension of that work.
- In the current study the applicant will now determine (i) to what degree this therapeutic window can be extended and (ii) how GMP grade cells will fare in this approach, and (iii) rate how human fetal cells compare to human ES cell derived cells and (iv) improve cell engraftment through immune suppression. The goals are a logical extension of the initial work and need to be done.
- The applicant is extremely aware of issues of heterogeneity in grafted cell populations, finding the best candidate cell and identifying robust readouts. It is only through this methodical and careful analysis that a stem cell transplantation approach has a chance to move forward.
- The PI has a great previous record of performance on CIRM grants.

Concerns

- TBI is an important topic but this may not be a way to treat it (i.e. stem cells may not be where to look).
- The proposal does not address potential long-term roadblocks that could conceivably make all stem cell TBI treatments impossible: immune suppression and delivery. However, these issues may be overcome, and the present work should lead to reagents, methods, results, and trained investigators, that can set the stage for addressing these issues later in other research projects.
- Local injection for a multifocal disease is a problem for this grant. Injecting cells into multiple sites in the brain of the patient is not feasible.
- Immunosuppression requirement is worrisome for feasibility.
- Significant immunosuppression required to engraft cells poses a barrier to translation.
- Need for NK depletion in mice raises concerns about translatability.
- Soft milestones without quantification of read-outs.
- Measurement of decrease in lesion volume for the milestones would go a long way toward improving the vague milestones.
- Preliminary data do not appear to be robust or compelling.

Additional Comments

- Please consult with a statistician before starting the work. It could be a fairly quick consult, but there are some minor issues with proposed statistical testing that could be improved (i.e. the issue of multiple test correction).

DISCOVERY

Application #	DISC2-09633
Title (as written by the applicant)	Human embryonic stem cell-derived satellite-like cells to treat respiratory insufficiency in children with severe and intermediate congenital NEM
Research Objective (as written by the applicant)	The goal of this project is to develop a muscle satellite-like cell as a potential allogenic stem cell therapy delivered to the diaphragm that could improve the medical condition of patients with NEM.
Impact (as written by the applicant)	A satellite-like cell would be an “off-the-shelf” cell therapeutic immediately available for patients diagnosed with NEM which is critical for addressing respiratory issues as quickly as possible.
Major Proposed Activities (as written by the applicant)	• In vitro optimization, establishment of production and freeze/thaw processes, and in vivo validation of candidate satellite-like cell subpopulations. • In vitro proof-of-concept efficacy studies of satellite-like cells using in vitro NEM models. • Early preclinical efficacy using immunodeficient mouse model of NEM and safety assessment in mouse teratoma formation assay.
Statement of Benefit to California (as written by the applicant)	Nemaline myopathy (NEM) is a debilitating muscle disease for which there are currently no effective treatments. Our company is dedicated to the use of human stem cell based disease modeling and optimization of a hESC derived cell therapeutic with the aim to accelerate a stem cell therapy for NEM, muscular dystrophies, neuromuscular disorders, and acute muscle injuries.
Funds Requested	$1,718,500
GWG Recommendation	***Tier 2: Not Recommended for funding***

Scoring Data

Final Score: --

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

Mean	--
Median	--
Standard Deviation	--
Highest	--
Lowest	--
Count	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	13	0
Is the rationale sound?	0	14	0

DISCOVERY

Is the proposal well planned and designed?	0	14	0
Is the proposal feasible?	0	14	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

- This proposal will address unmet needs to develop muscle satellite-like cell replacement therapy for patients with Nemaline myopathy (NEM).
- The project is starting from the very beginning of finding a good way to make satellite-like cells (including ways to freeze them).

Concerns

- The proposal deals mostly with incremental improvements to in vitro differentiation of human ESCs.
- It is not clear how the proposal will aid in translational issues for this disease indication.
- The application provided no preliminary results to support feasibility.
- There is a lack of evidence that these cells have any *in vivo* regenerative potential, even when injected directly in the muscle.
- The research plan does not properly address the biological question of targeting the diaphragm and improving respiratory function.
- Targeting the diaphragm is a much higher bar and there is no evidence this can be achieved.
- It is not clear why repair of the mutation in cells will not be performed. This is a big drawback of the proposed approach.
- It is unclear why NEM cells lines will be both created (ACTA1 mutant Genea094-NEM3 and Genea042-NEM3 lines that are isogenic to their parent normal cell lines) and studied *in vitro* in this proposal.
- Acta1 H40Y is a dominant mutation. It is not clear how (or how much) wt protein is needed to “restore” muscle function.
- The alternative approaches seem drastic. For example, if rescue is limited, mutant satellite cells will be inhibited by first radiation pre-treatment and muscle damage before injection.
- No evidence is provided that the cells have capacity to function.

DISCOVERY

Application #	DISC2-09635
Title (as written by the applicant)	Designing a cellular niche for transplantation of human embryonic stem cell-derived beta cells
Research Objective (as written by the applicant)	The expected outcome of these studies is a cellular therapeutic for Type I Diabetes: engineered human islets for transplant into patients, surpassing the function of beta cells or progenitors alone.
Impact (as written by the applicant)	The proposed studies would address key bottlenecks in cell replacement therapy for Type I Diabetes -- issues with cellular engraftment, survival, and function -- enabling optimized delivery in vivo.
Major Proposed Activities (as written by the applicant)	• Determine the optimal composition of human embryonic stem cell (hESC)-derived engineered islets in vitro. • Define key pathways underlying the mechanisms of niche-induced maturation of hESC-derived beta-like cells. • Demonstrate function of engineered islets in vivo in immunodeficient animal models of type I diabetes.
Statement of Benefit to California (as written by the applicant)	Type I Diabetes (T1D) is a significant burden in California, especially for children; according to estimates provided by the California Diabetes Program, ~2.3 out of every 1,000 children between the ages of 5-19 in California had diagnosed diabetes in 2008, with 83% having T1D. Research proposed here would represent a significant step towards the holy grail of T1D treatment: a therapy for patients without the need for the administration of insulin, frequent blood testing, or immunosuppression.
Funds Requested	$2,006,076
GWG Recommendation	***Tier 1: Recommended for funding***

Scoring Data

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.

Mean	88
Median	88
Standard Deviation	3
Highest	93
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	1	0
Is the rationale sound?	13	1	1

DISCOVERY

Is the proposal well planned and designed?	12	2	1
Is the proposal feasible?	12	3	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 investigator is a promising rising star in the field of stem cell-derived insulin-secreting cell products and the work proposed needs to be done.
- Outstanding preliminary outcomes with the addition of mesenchymal and endothelial cells.
- Microwells appear to be an excellent way to provide uniformity of islet composition.
- Reviewers were impressed by the preliminary data shown in Fig. 4 indicating that engineered immature beta cells (IBCs) can show such a high index by using small molecules.

Concerns

- The proposal is overambitious. The applicant should focus on the strengths of the preliminary data and downsize the aims to what can be reasonably achieved.
- Care needs to be taken not to get lost in the complexities of adding various niche components to partially differentiated beta cells, including endothelial cells, mesenchyme, pericytes, smooth muscle cells, fibroblasts, and/or nerves.
- In Aim 1 experiment 2 the target size and the composition ranges desired are not defined.
- Aim 1.1 lacks novelty and would produce results that are redundant with published literature (Bader E. Nature 2016, Brissova M. JHC 2005, Steiner JS Islets 2010, Kim A. Islets 2009, Kilimik G. Islets 2012, Otonkoshi T. Diab Ob Met 2008, just to mention a few).
- The last portion of Aim 2 Experiment 1 is overambitious, proposing to (1) screen an even larger pool of small molecules for niche-like signaling to IBC; (2) include 'various' combinations of ECM proteins; and (3) do RNA-Seq experiments to further generate candidate signaling pathways. Because no candidates for analysis are provided this sounds like a fishing expedition' and could be simplified or completely eliminated from the proposal.
- There is insufficient discussion about the need for immunoisolation devices or for immunosuppression to prevent autoimmunity.
- Microwell aggregation is a key innovation but scaling up might be a bottleneck for translation to human therapy.
- Scalability of the procedure to reaggregate cells using microwells is questionable since millions of clusters are needed to reverse T1D in patients.
- The limitations of the current design should have been highlighted to motivate further work to improve upon these exciting results; for example, whether cells generated with this design display perfusion results that are comparable to human islets or is further refinement needed.
- Sorting the other islet niche cells (for reaggregation with IBC) from cadaveric pancreatic islets is not very feasible if the end-point application of the proposed product is transplantation. The idea of using SC-derived insulin-secreting cell products is to have an inexhaustible cell source and not depend on the poor availability of cadaveric pancreata.
- There are several issues associated with the 'delay' in diabetes reversal with the most worrisome being (i) the signals in mouse that drive IBC full differentiation may be different in humans, and this would be unpredictable during preclinical studies for IND application; (ii) the cells are 'changing' during implantation so the product that is validated before transplantation will be different that the product in the patient after transplantation.
- What's the efficiency of the CRISP/Cas9 gene editing technique on IBCs or on beta cells?

Additional Comments

- Addition of small compounds promoting beta cell differentiation or GSIS might be very beneficial.
- Important future direction: " In future work, engineered islets may be encapsulated to protect them from autoimmune attack."
- Aim 1.1 is very descriptive. So this reviewer recommends to review the literature and define the design criteria for the optimal beta cell niche that more closely recapitulates the in vivo situation and use those data as input (optimization criteria) for Aim 1.2.

- As alternative site for transplantation in diabetic mice the investigator proposes to use the omental fat and references a study done in rats. Note that the mouse omentum is much smaller, thinner and less vascularized than the rat omentum so not an ideal site for transplantation of insulin-secreting cell products. This reviewer suggests to use the mammary fat pad in female mice or the epididymal fat pad in male mice.

DISCOVERY

Application #	DISC2-09637
Title (as written by the applicant)	Genome Editing to Correct Cystic Fibrosis Mutations in Airway Stem Cells
Research Objective (as written by the applicant)	Gene corrected autologous airway epithelial stem cells from patients with cystic fibrosis to be used as cell and gene based therapy for chronic sinus disease
Impact (as written by the applicant)	The proposed studies would provide an innovative, readily applied primary stem cell based approach with gene correction to treat chronic sinusitis in CF, a debilitating airway disease.
Major Proposed Activities (as written by the applicant)	• Identification of active CRISPR/Cas9 nucleases that can edit the human CFTR gene • Develop a direct mutation correction genome editing approach for the delta F508 mutation and a “Universal CFTR” correction system for the other CF causing mutations • Identification of a genome editing delivery system for primary airway stem cells from CF patients • Genome editing by homologous recombination in CF patient derived airway stem cells • Test physiologic function of gene corrected CF airway stem cells when converted into organoids • Xenotransplantation of gene corrected CF airway stem cells into NSG mice
Statement of Benefit to California (as written by the applicant)	Cystic fibrosis (CF) is one of the most common genetic diseases in California. There is no curative therapy for CF and CF patients spend a lifetime focused on mitigating the symptoms of their disease. Moreover, the costs of treating a single CF patient are enormous. Thus, the benefit to California if this proposal is successful is that it would improve the lives of its citizens (both patients and family members) while simultaneously decreasing the societal costs that this disease inflicts.
Funds Requested	$2,201,136
GWG Recommendation	***Tier 1: Recommended for funding***

Scoring Data

Final Score: 85

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

Mean	85
Median	85
Standard Deviation	3
Highest	90
Lowest	80
Count	15
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	10
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?	12	0	3
Is the rationale sound?	10	0	5
Is the proposal well planned and designed?	10	1	4
Is the proposal feasible?	8	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

- The goal of this proposal is to correct the CFTR mutation in airway basal cells of patients with Cystic Fibrosis as a potential source of cell-based therapy. This is an exciting and important proposal based on sound scientific rationale. The team is well-equipped to embark on this endeavor.
- Significance and novelty of project as well as expertise of team of investigators are strengths of this proposal.
- Proposal addresses important unmet need, includes an outstanding team, and there is excellent theory behind proposal.
- Targeting the CFTR gene *in vivo* (or *in vitro* in patient-derived somatic stem cells) could directly lead to incredible improvement in patient care.
- Correction using genetic approach regardless of mutation type is a strength.
- Very ambitious proposal but with high potential.
- Milestones 1 and 2 will likely be achieved.

Concerns

- CFTR correction is challenging and hasn't been achieved yet.
- Although the team have extensive expertise in gene-editing techniques, the efficient gene-correction of human bronchial epithelial cells is likely to be very challenging based on the lack of success to date.
- The decision to not include a method of purifying or enriching for successfully gene-corrected basal cells is a major limitation in the general applicability of this tool for the next translational experiments if it is successfully developed in the first place.
- There is insufficient focus on the cell types that are successfully gene-corrected and how both the process of gene-editing and the continued culture of these cells affects their phenotype and, ultimately, suitability of transplantation.
- Engraftment into the airway epithelium is not a trivial undertaking and the likelihood of this model working, in such a short time frame and with no reported preliminary success, is very low.
- This reviewer has concerns about the feasibility for a timeline of 2 years.
- Timeline to achieve proposal is ambitious.
- The feasibility was the issue for this reviewer. It's not clear what cells will be corrected and how *in vitro* culture will affect its cells.
- The applicant should describe a method to remove upper airway stem cells in human subjects prior to transplanting the modified cells.
- The proposed approach will correct either delF508 (found in 85% of CF patients) or a “universal” strategy in which a cDNA will be placed at the CFTR locus. It is not clear why two approaches are needed since universal approach will cure the delF508 mutation.
- Cell engraftment is challenging and failures of this are not considered.
- The choice of the nose as the implant site will not be as informative as placement into the lung.
- The proposal does not provide preliminary data that epithelial cells are corrected and that they survive after transplantation.

DISCOVERY

Application #	DISC2-09645
Title (as written by the applicant)	Dynamic scaffolding system to enhance lineage-specific differentiation and downstream functionality of induced pluripotent stem cells
Research Objective (as written by the applicant)	This study will develop a stem cell culture system which will improve the differentiation efficiency and downstream functionality of stem cells for enhanced therapeutic applicability.
Impact (as written by the applicant)	It will improve current inefficient stem cell differentiation methods to produce clinically applicable cells in a cost-effective manner.
Major Proposed Activities (as written by the applicant)	• Optimize multi-functional scaffolds for enhanced piezoelectric properties and biocompatibility. • Develop a high-throughput cell culture system with on-demand mechanically tunable scaffolds. • Determine the effects of stage-dependent temporal control of the mechanical microenvironment on stem cell differentiation.
Statement of Benefit to California (as written by the applicant)	This project seeks to advance the safety and effectiveness of the use of stem cells for regeneration of damaged tissues in patients by developing a novel technology. The project speaks directly to the mission of CIRM, particularly to improve human health of California's rapidly growing population by improving stem cell-based therapies. The commercialization of the full-scale system would benefit the people in California with the financial impact of increased employment and tax revenues.
Funds Requested	$804,254
GWG Recommendation	***Tier 2: Not recommended for funding***

Scoring Data

Final Score: 84

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

Mean	83
Median	84
Standard Deviation	5
Highest	90
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?	8	1	5
Is the rationale sound?	8	3	3
Is the proposal well planned and designed?	8	2	4
Is the proposal feasible?	7	1	6

DISCOVERY

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 applicant proposes to develop a novel cell culture system that may improve the yield of stem cell (SC) differentiation into the desired phenotype increasing safety and decreasing costs of production. By improving the yield of SC differentiation and decreasing risk of teratoma formation at lower costs and in a more time-effective manner, the proposed technology may increase the applicability of SC-based therapies.
- The dynamic changes of the mechanical environment are important.
- The proposal presents a high quality bioengineering approach.
- The applicant has made significant revisions since the last cycle.
- The new focus on pancreatic beta cells makes it more translational.

Concerns

- It is not clear that the proposed bioengineering approach substantially improves differentiation.
- There is limited evidence that this approach makes significantly better beta cells.
- Functional data are not provided to show a correlation between stiffness of scaffold substrates and functionality (GSIS) of primary human islets or SC-derived insulin-secreting cell products.
- Preliminary data are not provided to demonstrate that coating the proposed optimized fibers with PCL through coaxial electrospinning does not modify the piezoelectric properties (i.e. the spatiotemporal stiffness of the resulting scaffolds as shown in Fig. 12).
- Preliminary data are not provided to demonstrate that the optimized electrospun fibers with comparable stiffness to scaffolds shown in Fig. 9 can modulate the differentiation of SCs depending on scaffold stiffness and independently of fiber composition.
- The preliminary data clearly show that the proposed technology can impact all stages of SC differentiation and potentially the quality of the end product, though only data on MIN6 insulinoma cells cultured as a monolayer rather than cell clusters (like islets are) are provided (no data on primary human islets or SC-derived insulin-secreting cell products).

DISCOVERY

Application #	DISC2-09649
Title (as written by the applicant)	A treatment for Zika virus infection and neuroprotection efficacy
Research Objective (as written by the applicant)	We propose to determine the impact of the Zika virus during human neurodevelopment and to test a FDA-approved therapeutic candidate to treat Zika infection.
Impact (as written by the applicant)	A drug to treat/cure Zika infection and for neuroprotection.
Major Proposed Activities (as written by the applicant)	• To determine the molecular and cellular alterations caused by the Zika virus in the human developing brain and to validate a potential treatment for Zika infection. • To re-purpose a therapeutic drug to treat Zika infection and for neuroprotection using in vivo models. • To prepare and organize a clinical trial for Zika infection in a target population using a repurposed FDA-approved anti-viral drug.
Statement of Benefit to California (as written by the applicant)	The recent outbreak of Zika virus prompted the WHO to declare a public health emergency of international concern due to the link between infected pregnant women and microcephalic babies. The virus is spreading quickly and cases of Zika was already reported in California. This proposal will test a FDA-approved drug repurposed to neutralize the virus deleterious consequences in human brain cells. The experiments are designed to learn about the long-term consequences of the virus infection.
Funds Requested	$2,117,880
GWG Recommendation	***Tier 1: Recommended for funding***

Scoring Data

Final Score: 93

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

Mean	93
Median	93
Standard Deviation	3
Highest	100
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?	12	0	3
Is the proposal well planned and designed?	14	0	1

DISCOVERY

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 highly relevant proposal that addresses the increasing concern of Zika. It is of particular importance that the applicant provides a direct pass to a potential therapeutic for already infected individuals.
- This application focuses on a Zika strain that is associated with birth defects and microcephaly and is 90% similar to the most prominently studied Zika strain. This gives this application a serious advantage in respect to relevance.
- This is a very important topic that needs therapeutic interventions.
- The preliminary studies done are very strong, and the experimental plan is well-thought out.
- Preliminary data is very strong both for the *in vitro* human NSC models and for the *in vivo* preclinical mouse model.
- Lead compound is already FDA approved and the PI has a detailed plan for moving to pre-IND and phased trials in Brazil.
- The experimental details are well-lined out and the design is appropriate.
- The applicants are proposing in Aim 1 to test the drug on a number of readouts of neural development and function in the cortex using their well establish organoid system. Aim 2 is preclinical testing of that drug using their unique *in vitro* and *in vivo* models.
- The response to concerns raised in previous views has been excellent.

Concerns

- The testing of the candidate drug has not been done in the pregnancy model of Zika that the applicant established. Instead, they injected Zika directly into the tail vein and then tested the efficacy of the drug in respect to neuronal cell death. This is a very different model of Zika infection than the pregnancy transfer to the developing fetus and thus it remains unclear whether the drug will have any benefit in the transmission model.
- It is not clear to whom and at what time this drug would be administered. That is, does the applicant propose to give the drug during pregnancy and can the drug cross the placental barrier?
- There is a probable need for combination therapy, but RNA-seq analysis may not lead to in-depth understanding.

DISCOVERY

Application #	DISC2-09654
Title (as written by the applicant)	Discovery of therapeutics for Huntington's Disease
Research Objective (as written by the applicant)	Research seeks to identify candidate drugs to treat Huntington's disease by using hESCs grown in a confined space to reproduce cell interactions between cells that occur normally during development
Impact (as written by the applicant)	Potential to revolutionize the drug screening process; the approach described can be potentially applied to any genetic disease, thus expanding its impact beyond just Huntington's disease
Major Proposed Activities (as written by the applicant)	• Use of our proprietary technology to identify compounds that can affect changes caused by the Huntington mutation in human embryonic stem cells • Testing of compounds identified in Activity #1 to see which ones can also enhance the survival of Huntington's disease human cortical neurons generated from human embryonic stem cells • Testing of compounds identified in Activity #1 to see which ones can also enhance the survival of Huntington's disease human medium spiny neurons generated from human embryonic stem cells
Statement of Benefit to California (as written by the applicant)	There are two main benefits for California: First, we will introduce a technology, which does not yet exist outside of my laboratory. This complements the mission of CIRM. Because our platform has a wider application than just modeling HD phenotypes, we anticipate the creation of new industries using these methods. Secondly, an estimated 40,000 Californians struggle with this incurable disease. Any improvement to their conditions will be of tremendous value for them, and their loved ones.
Funds Requested	$1,399,800
GWG Recommendation	***Tier 2: Not recommended for funding***

Scoring Data

Final Score: 60

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

Mean	60
Median	60
Standard Deviation	0
Highest	60
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

DISCOVERY

Does the proposal have a potential for impact?	3	9	3
Is the rationale sound?	0	13	2
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 application is by a strong PI and proposes an innovative cell source.

Concerns

- The assay itself may be providing interesting information about the developmental biology that occurs in individuals who eventually will develop HD, but this may be very different than providing treatments that would be initiated after disease symptoms have manifested. These are hypotheses that need to be tested and not just assumed to be correct.
- Demonstration that the disease on the dish is relevant to the disease is not provided and there is no plan for *in vivo* validation.
- There is no demonstration that the *in vitro* assay outcomes are relevant to HD *in vivo*, and no testing of the candidate drugs *in vivo*.
- There does not appear to be any planned testing *in vivo*, with the suggestion that one could go directly from screens *in vitro* to use in the patient.
- The proposal lacks validation of the results of the screens to other models such as *in vivo*.
- It is unclear whether the results will be therapeutic.
- Serious concerns with the sole focus on iPSC cells as a model for HD.

DISCOVERY

Application #	DISC2-09656
Title (as written by the applicant)	Direct Reprogramming of fibroblasts into myogenic cells by using chemical compounds
Research Objective (as written by the applicant)	Our objective is to develop a chemical cocktail to reprogram autologous fibroblasts into myogenic cells to treat traumatic muscle injury and muscle dystrophy.
Impact (as written by the applicant)	A bottleneck for muscle regeneration is the lack of autologous myogenic cells. The chemical cocktail and reprogrammed autologous myogenic cells can be used to promote muscle regeneration.
Major Proposed Activities (as written by the applicant)	• To establish the chemical cocktail to reprogram fibroblasts into myogenic cells. • To purify and characterize the reprogrammed human myogenic cells in vitro. • To investigate the therapeutic effect of transplanted myogenic cells in muscle regeneration. • To determine the efficiency of in situ cell reprogramming by the controlled release of the chemical cocktail.
Statement of Benefit to California (as written by the applicant)	Muscle regeneration is often compromised by aging, excessive trauma, injury, or genetic defect as in muscular dystrophies. A bottleneck is the lack of autologous myogenic cells. If achieved, our project will result in a chemical cocktail to reprogram fibroblasts into myogenic cells and myogenic cells that can be transplanted for muscle regeneration, which will lead to new therapies to patients with muscle injury, loss, atrophy and dystrophy and benefit the patients in California.
Funds Requested	$2,132,926
GWG Recommendation	***Tier 2: Not recommended for funding***

Scoring Data

Final Score: --

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

Mean	--
Median	--
Standard Deviation	--
Highest	--
Lowest	--
Count	15
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?	3	8	4
Is the rationale sound?	0	14	1

DISCOVERY

Is the proposal well planned and designed?	1	10	4
Is the proposal feasible?	0	11	4

Reviewer Comments

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

Strengths

- If successful, the technology could develop human myogenic cells from dermal fibroblasts with prospects of using in cell therapies.

Concerns

- The concept is attractive but the application has major flaws, including 1) lack of evidence that satellite cells can be generated through direct reprogramming, 2) lack of evidence this reprogramming strategy will work for human fibroblasts, 3) lack of evidence that gene editing can be efficiently done in fibroblasts, and 4) lack of clarity and focus.
- It is not clear how the proposal could be translated to clinical treatments as most *in vivo* experiments are in the mouse.
- Insufficient plans and details on how effective and safe these cells could be for translation to human patients compared to *in vivo* derived and expanded muscle satellite cells or cells derived from ESC/IPSCs.
- Intriguing idea but overambitious. Needs more preliminary data for feasibility.
- Unclear in humans if *in vivo* reprogramming of fibroblasts into muscles will result in any benefit to patients since the “new” muscles cells would contain the same genetic defects as the cells that they would be replacing.
- It is not clear how fibroblasts will be specifically targeted by injection (injection is into damaged muscle cells).
- The in vivo approach appears to have limited application for disease prevention. It could aid in injury recovery (this is not discussed in the context of human therapy).
- There is no evidence provided that appropriate cells are targeted or efficacious.
- The cocktail development may take longer than 2 years thereby reducing feasibility.