QUEST AWARDS

$21,057,289 GWG RECOMMENDED

APP #	TITLE	BUDGET	FUND?	SCORE (MEDIAN)	Mean	SD	Score Range Low	Score Range High	Number of GWG Votes Y	Number of GWG Votes N	Resubmission	Previous CIRM Funding	Disease Indication	Product Type	Approach
DISC2-10591	Preclinical development of an immune evasive islet cell replacement therapy for type 1 diabetes	$1,470,987	**Y**	**90**	91	4	85	95	13	0	N	Y	Type 1 diabetes	Cell therapy	Universal donor cell line
DISC2-10524	Genome Editing of Sinusoidal Endothelial Stem Cells for Permanent Correction of Hemophilia A	$2,182,193	**Y**	**90**	90	1	85	90	15	0	N	N	Hemophilia A	Gene therapy	In vivo correction of factor VIII gene
DISC2-10679	Towards hepatocyte cell replacement therapy: developing a renewable source of human hepatocytes from pluripotent stem cells	$2,201,136	**Y**	**90**	90	2	85	95	15	0	Y	N	Liver failure	Cell therapy	Renewable hepatocytes from hPSCs
DISC2-10748	Engineering Lifelong Cellular Immunity to HIV	$1,701,178	**Y**	**90**	89	2	85	92	15	0	N	Y	HIV infection	Gene-modified cell therapy	Modify blood stem cells to target HIV
DISC2-10714	iPS Glial Therapy for White Matter Stroke and Vascular Dementia	$2,096,095	**Y**	**89**	88	2	85	90	14	0	Y	Y	Vascular dementia	Cell therapy	Glial enriched progenitors from iPSCs
DISC2-10604	Stimulating endogenous muscle stem cells to counter muscle atrophy	$2,198,687	**Y**	**88**	87	5	70	90	14	1	N	Y	Muscle atrophy	Small molecule	Drug to stimulate muscle stem cells
DISC2-10753	Generation and in vitro profiling of neural stem cell lines to predict in vivo efficacy for chronic cervical spinal cord injury.	$1,575,613	**Y**	**85**	86	6	75	95	11	4	N	N	Spinal cord injury	Cell therapy	Human neural stem cell lines
DISC2-10751	Silicon Nanopore Membrane encapsulated enriched-Beta Clusters for Type 1 Diabetes treatment	$1,113,000	**Y**	**85**	85	2	81	90	13	2	N	N	Type 1 diabetes	Cell encapsulation device	Transplantion of beta cells in device
DISC2-10695	Identification and Generation of Long Term Repopulating Human Muscle Stem Cells from Human Pluripotent Stem Cells	$2,184,000	**Y**	**85**	84	3	80	90	11	4	N	N	Muscle disorders	Cell therapy	Muscle stem cells from hPSCs
DISC2-10747	Targeting Cancer Stem Cells in Hematologic Malignancies	$2,167,200	**Y**	**85**	84	3	75	87	12	3	N	N	Acute myeloid leukemia	Monoclonal antibody	Antibody targets cancer stem cells
DISC2-10559	Development of immune invisible beta cells as a cell therapy for type 1 diabetes through genetic modification of hESCs	$2,167,200	**Y**	**85**	83	5	70	90	11	4	N	Y	Type 1 diabetes	Cell therapy	Non-immunogenic beta cell progenitors
DISC2-10599	Translational Imaging Tools for Human Regenerative Therapies	$1,100,400	**N**	**84**	83	2	80	85	7	8	N	Y			
DISC2-10665	Neural Stem Cell Relays for Severe Spinal Cord Injury	$2,100,581	**N**	**80**	82	3	80	90	5	10	N	Y			
DISC2-10647	Development of PEG-PTN for Hematopoietic Regeneration	$960,380	**N**	**80**	81	7	70	90	7	8	Y	Y			
DISC2-10433	Development of a new therapeutic for directing target specific stem cell migration and treatment	$1,906,900	**N**	**80**	80	2	75	82	0	15	Y	Y			
DISC2-10626	Develop iPSC-derived microglia to treat progranulin deficient Frontotemporal Dementia	$1,929,714	**N**	**80**	80	3	75	85	3	11	Y	N			
DISC2-10525	Development of a Cellular Therapeutic for Treatment of Epilepsy	$1,616,536	**N**	**80**	78	9	60	90	7	8	N	Y			
DISC2-10546	Exosomes from iPSC-derived cardiomyocytes for porcine model of myocardial injury	$2,180,383	**N**	**78**	79	10	55	90	6	8	N	Y			
DISC2-10562	Treating advanced retinal degeneration diseases using a tissue engineered co-graft	$1,883,051	**N**	**78**	74	7	60	80	0	15	N	Y			
DISC2-10745	Dynamic scaffolding system to enhance phenotype-specific differentiation and downstream functionality of induced pluripotent stem cells	$802,125	**N**	**75**	78	8	70	95	3	12	Y	N			
DISC2-10460	Mesenchymal stem cell extracellular vesicles as therapy for pulmonary fibrosis	$2,013,760	**N**	**75**	75	1	70	75	0	14	N	N			
DISC2-10566	Off-the-shelf hypo-immunogenic iPSC-derived CAR-T-cells for allogeneic therapies	$1,916,250	**N**	**75**	75	4	70	85	1	14	N	N			
DISC2-10678	Adipose Derived Stem Cells Transduced With a Lentiviral Vector To Enhance Bone Repair	$2,124,849	**N**	**75**	74	4	70	80	0	15	N	N			
DISC2-10773	A screen for drugs to protect against chemotherapy-induced hearing loss, using sensory hair cells derived by direct lineage reprogramming from hiPSCs.	$1,167,600	**N**	**75**	74	2	70	75	0	15	N	N			
DISC2-10609	Development of dual gate chimeric antigen receptor T cell therapy for lethal neuroendocrine prostate cancer	$1,540,221	**N**	**75**	73	3	70	75	0	15	Y	Y			
DISC2-10507	A comprehensive strategy to non-invasively monitor the pharmacokinetics of stem cell-derived therapies in patients	$1,072,581	**N**	**75**	71	7	60	80	0	15	N	N			
DISC2-10456	Manipulation of the skeletal stem cell niche for articular cartilage regeneration	$2,145,611	**N**	**70**	71	3	65	75	0	15	N	N			

APP #	TITLE	BUDGET	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Resubmission	Previous CIRM Funding	Disease Indication	Product Type	Approach
DISC2-10749	iPSC derived neural progenitor cell therapy for juvenile macular dystrophy	$1,832,527	**N**	**70**	66	7	50	75	0	15	Y	N			
DISC2-10478	Exosomes from cardiac progenitor cells targeted to treat heart failure	$1,677,130	**N**	**65**	66	7	60	80	0	14	N	N			
DISC2-10487	Assessment of Novel Depots of Adipose-Derived Stem Cells for Chronic Rotator Cuff Injury	$1,870,533	**N**	**65**	66	4	60	70	0	15	N	N			
DISC2-10605	Stem Cell-based Modeling and Therapeutic Targeting of IDH Mutant Gliomas	$2,212,924	**N**	**65**	64	4	60	75	0	15	Y	N			
DISC2-10623	Discovery of novel and personalized treatments for Parkinson's disease using IPSC-derived dopaminergic neurons	$1,399,076	**N**	**65**	64	12	40	90	1	14	N	N			
DISC2-10733	Engineered mesenchymal stem cells for combinatorial cancer immunotherapies	$1,831,126	**N**	**65**	64	11	30	75	0	15	Y	N			
DISC2-10596	Development of Vasculature from iPSCs	$1,855,539	**N**	**-**	-	-	-	-	0	15	Y	N			
DISC2-10715	Spinal multisegmental stem cell delivery for treatment of amyotrophic lateral sclerosis.	$2,126,070	**N**	**-**	-	-	-	-	0	15	N	N			
DISC2-10666	Engineering Live Meniscus Tissue by Electrospinning and Electrospraying Stem Cells	$1,876,585	**N**	**-**	-	-	-	-	0	15	Y	Y			
DISC2-10473	Homing/Efficacy of a Novel Pluripotent Non-Tumorigenic Human Adult Stem Cells Isolated from Adipose Tissue in Acute Myocardial Infarction Mice Models	$2,171,244	**N**	**-**	-	-	-	-	0	15	N	N			
DISC2-10667	Functional human islet-like organoids (HILOs) as therapy for Type 1 Diabetes	$2,491,874	**N**	**-**	-	-	-	-	0	14	N	Y			
DISC2-10556	Promoting myelin repair in Multiple Sclerosis via N-acetylglucosamine induced oligodendrocyte differentiation from neural stem/progenitor cells.	$939,160	**N**	**-**	-	-	-	-	0	15	N	Y			
DISC2-10709	Novel anti-arrhythmic agents in cardiac cell-based therapy	$2,200,800	**N**	**-**	-	-	-	-	0	15	Y	N			
DISC2-10421	SEMA4D as a predictive biomarker for brain metastasis	$1,077,764	**N**	**-**	-	-	-	-	0	15	N	N			
DISC2-10441	Novel Tools for Drug Discovery: Generation of Hematopoietic Stem and Progenitor Cells from From Primary Human Leukemia-derived iPSCs	$587,672	**N**	**-**	-	-	-	-	0	15	N	N			
DISC2-10729	Manipulation of oxygen and pressure to increase neural cell differentiation efficiency and promote functional maturation	$698,400	**N**	**-**	-	-	-	-	0	15	N	Y			

DISCOVERY

Application #	DISC2-10591
Title (as written by the applicant)	Preclinical development of an immune evasive islet cell replacement therapy for type 1 diabetes
Research Objective (as written by the applicant)	We will produce a universal donor cell (UDC) line by gene editing an embryonic stem cell line. Cell therapies produced from the UDC line will not be rejected by a patient's immune system.
Impact (as written by the applicant)	The UDC line will address the bottleneck of patient immunity that is currently slowing development of many potential cell therapies. It will first be tested in a type 1 diabetes cell therapy.
Major Proposed Activities (as written by the applicant)	• Produce banks of UDC that are of suitable quality for use in manufacturing therapeutic cells for clinical trials. • Demonstrate that pancreatic cells produced from UDC and implanted into rodents can secrete insulin in response to glucose. • Demonstrate that pancreatic cells produced from UDC evade immunity, i.e. are destroyed much less efficiently than the unmodified cells in immunological tests. • Demonstrate function of a gene added into the UDC as a "safety switch". This safety gene causes implanted cells to die when a specific drug is taken and is a precautionary part of product development.
Statement of Benefit to California (as written by the applicant)	The universal donor stem cell line would firstly be used to help the thousands of Californians with insulin-requiring diabetes, but soon thereafter would be applied to other substantially unmet medical needs. Cell therapies have the potential to restore a relatively normal life to patients and their families, extend patients' lives, and dramatically reduce the state's health care burden. This would represent a tremendous achievement and asset for California, its taxpayers, and CIRM.
Funds Requested	$1,470,987
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

Scoring Data

Final Score: 90

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

Mean	91
Median	90
Standard Deviation	4
Highest	95
Lowest	85
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	0

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have the necessary significance and potential for impact?	13	0	1
Is the rationale sound?	12	1	1

Is the proposal well planned and designed?	13	0	1
Is the proposal feasible?	12	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

- Strong preliminary results and clear path to clinical translation
- The proposed work will take advantage of a clinical grade hESC line to be modified as previously published
- A major strength of the proposal is the team and collaborators, who have key expertise in creating cells that express HLA-E as their only surface HLA class I molecule; this could go a long way to protect beta cells form autoimmunity and allograft rejection
- For safety purposes, there is a plan to build in a “kill switch”
- Able to produce universal donor cells with minimal HLA expression
- Gene editing is an innovative approach
- The data show that they can generate modified donor cells that prevents NK-mediated lysis in vitro and in vivo
- The gene edited donor cells are not recognized as allogenic unlike WT cells in vitro and in vivo using human EB-primed CD8 T cells
- Cells differentiated from the gene edited cells are stable
- High quality assays and protocols for generation and characterization of immunogenicity of the cells are described
- IND supported by preliminary data showing feasibility
- Overall well-constructed, in particular the quality of the in vitro and in vivo assays and the discussion about the humanized mice: outstanding
- Outsourcing manufacturing of genetically modified cells for clinical translatability is in line with CIRM mission to accelerate product development for patients

Concerns

- Concerns regarding safety
- Reduction of immunity may set up conditions for malignant transformation
- The genetic manipulation effect on function of cells may be problematic
- The claim that cells differentiated from the gene edited donor cells are functional is not supported by data
- The PI is not clear about which humanized mouse model will be used to the test the immune-privilege capacity of the hESC-derived beta-cells; several options are put forward
- Using the device for some of the in vivo immune assays may not be ideal given the poor survival of the cells in the device; there may not be enough cells left for testing after implantation

DISCOVERY

Application #	DISC2-10524
Title (as written by the applicant)	Genome Editing of Sinusoidal Endothelial Stem Cells for Permanent Correction of Hemophilia A
Research Objective (as written by the applicant)	Therapeutic candidate to cure hemophilia A is AAV-based genome editing vector that corrects the disease-causing mutation in the factor VIII gene in patient stem cells to develop a permanent cure.
Impact (as written by the applicant)	Permanent correction of hemophilia A by editing mutations in the FVIII gene in stem cells. Develop a precise and efficient non-nuclease genome editing technology for editing somatic stem cells in vivo.
Major Proposed Activities (as written by the applicant)	• Identification of optimal genome editing vector for editing the FVIII gene in human endothelial cells, somatic stem cells and immortalized cells derived from hemophilia A patient. • Test successful in vitro genome editing in the human stem cells that give rise to the clotting factor VIII producing cells. • Demonstrate genome editing of the FVIII gene in human stem cells and their progeny, to provide proof of concept of the gene editing strategy for therapeutic correction of the mutation. • To identify the best genome editing vector for correcting xenotransplanted human stem cells in immune-deficient mice in vivo. • Functional evidence of genome editing of FVIII gene in regenerating mouse liver after partial hepatectomy. • Test therapeutic correction of hemophilia A in a dog model to obtain proof of efficacy of this genome editing strategy. This information will facilitate translation and discussions with the FDA.
Statement of Benefit to California (as written by the applicant)	Hemophilia A is an incurable, devastating inherited bleeding disorder caused by the lack of functional clotting factor VIII. The management of hemophilia A poses a large economic and quality of life burden. Twenty percent of all hemophilia patients live in California. We plan to develop a therapeutic candidate for the correction of the causative factor VIII mutations in stem cells using genome editing in order to develop a permanent cure for hemophilia A.
Funds Requested	$2,182,193
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

Scoring Data

Final Score: 90

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

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

Score Influences

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

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

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

Reviewer Comments

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

Strengths

- High impact on the practice of medicine
- Important clinical project
- Clever scientific approach
- Novel gene correction strategy
- The proposed work makes use an innovative adeno-associated virus (AAV) that allows for editing of targeted regions of the genome
- The proposed work benefits from a remarkable set of preliminary results demonstrating the high efficiency of on-target gene insertions that can be mediated by AAVHSV transductions, both using in vitro and in vivo models.
- Well-constructed and carefully thought out proposal
- Good group

Concerns

- The need for a target cell, likely within the liver, to be a stem cell would be beneficial, but the proposed work is not fully reliant on the use or modification of stem cells to induce the genetic repair
- It is not very clear whether in Aim 1E the use of hemophilia patient-derived B leukemia cell line was appropriate, as it was not stated whether these cells were expected to show expression of FVIII after gene correction; this issue was pointed out regarding the use of stem cells, as these cells might need to differentiate before FVIII expression could be detected
- Large program of work

DISCOVERY

Application #	DISC2-10679
Title (as written by the applicant)	Towards hepatocyte cell replacement therapy: developing a renewable source of human hepatocytes from pluripotent stem cells
Research Objective (as written by the applicant)	To develop a consistent and abundant source of transplantable human hepatocytes for transplantation.
Impact (as written by the applicant)	Developing an abundant and consistent source of human hepatocytes that can be used to treat patients with liver failure.
Major Proposed Activities (as written by the applicant)	• To determine the degree by which human pluripotent stem cell (hPSC)-derived hepatocytes engraft and restore liver function in mouse models of liver injury • To assess long-term safety of transplanted hepatocytes in vivo • To track long-term localization and cell-growth of transplanted hPSC-derived hepatocytes after transplantation into injured mouse livers • To profile cell-type specific surface markers expressed on hPSCs and hPSC-derived hepatocytes
Statement of Benefit to California (as written by the applicant)	Liver failure is one of the 12 leading causes of adult death in the U.S. The only long-term treatment for liver failure is to transplant a new liver, but there is a grim shortage in available livers, with many patients dying while awaiting a suitable liver. Our research aims to generate large numbers of human liver cells derived from stem cells that could one day be used to treat patients with liver disease and end-stage liver failure.
Funds Requested	$2,201,136
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

Scoring Data

Final Score: 90

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

Score Influences

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Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have the necessary significance and potential for impact?	14	0	0
Is the rationale sound?	13	1	0
Is the proposal well planned and designed?	14	0	0
Is the proposal feasible?	11	1	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 need for a product to replace transplantation liver donors is great
- High impact
- Very responsive to previous critiques
- Very likely to generate data useful for a clinical trial application
- Feasible as there is a wealth of data
- Approach for defining phenotypic markers for increasing differentiation yield
- Clever use of knock-in with correlation to cell surface phenotype
- Proposal to solve issues associated with purity and toxicity is well written
- Well-planned and rigorous study with proper controls
- Team: strong GMP production capability - high translational potential
- Quality of the team is excellent
- Excellent team
- Strong track record

Concerns

- If 6-month efficacy is not realized, the rest of the proposal becomes less relevant
- If the 6-month first milestone fails then everything that follows won't be feasible

DISCOVERY

Application #	DISC2-10748
Title (as written by the applicant)	Engineering Lifelong Cellular Immunity to HIV
Research Objective (as written by the applicant)	We aim to uncover a therapeutic approach to attempt to treat and potentially cure HIV infection using gene modified blood forming stem cells to enhance the immune response against HIV.
Impact (as written by the applicant)	The study will allow a potentially curative treatment for HIV infection, which currently doesn't exist. This will eliminate the need to administer antiviral medication for a lifetime.
Major Proposed Activities (as written by the applicant)	• We will test and identify an optimized chimeric antigen receptor (CAR) to modify blood forming stem cells to form cells that will target HIV infection using humanized mice. • We will achieve cell specific expression of the CAR in T cells and natural killer cells for better efficacy and safety in the cells that the molecule would work best in targeting HIV infection. • In a system that highly resembles humans, we will transplant large animals with several candidate chimeric antigen receptors to compare and test optimized transplantation strategies. • We will identify the best chimeric antigen receptor and the optimal transplantation protocol in HIV/SIV (SHIV) infected large animals, providing insight into using this therapy in HIV+ humans.
Statement of Benefit to California (as written by the applicant)	California ranks second in the nation in cases of HIV, with over 170,000 persons currently living with HIV with the direct healthcare cost to California approaching $1.8 billion annually. A curative treatment is therefore a high priority. A stem cell based therapy offers promise for this goal, by providing an inexhaustible source of protected, HIV specific immune cells that would provide constant surveillance and potential eradication of the virus in the body.
Funds Requested	$1,701,178
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

Scoring Data

Final Score: 90

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

Mean	89
Median	90
Standard Deviation	2
Highest	92
Lowest	85
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	15
(1-84): Not recommended for funding	0

Score Influences

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Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have the necessary significance and potential for impact?	14	0	0
Is the rationale sound?	14	0	0
Is the proposal well planned and designed?	14	0	0
Is the proposal feasible?	11	1	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 proposed work will develop an innovative approach to address an important unmet medical need, which is the eventual viral rebound of HIV-infected individuals that discontinue combination anti-retroviral therapy (cART)
- Good approach
- Strong design
- The work will make use of chimeric antigen receptor (CAR) T cells that target HIV infected cells, with the addition of a gene to interfere with T cell infection by HIV; this approach has the potential to provide lifelong immunity to HIV
- Good preliminary data
- The proposed work has a solid foundation and is supported by very strong preliminary results showing the team's ability to generate CAR transduced HSCs that can function in vivo, and show promising activity in HIV challenge models
- The PI has assembled a superb team of HIV experts and obtained critical collaborators for the important animal work
- Excellent team

Concerns

- As part of aim 2, it would have been important to consider the age of the large animal recipients as an additional test, as this might impact in the host thymic function which could affect the clinical translational capacity of the proposed approach
- Overambitious timeline

DISCOVERY

Application #	DISC2-10714
Title (as written by the applicant)	iPS Glial Therapy for White Matter Stroke and Vascular Dementia
Research Objective (as written by the applicant)	This cell line will target recovery in ischemic white disease, a progressive dementing condition with no current therapy by developing a new stem line, iPS-glial enriched progenitors (iPS-GEPs).
Impact (as written by the applicant)	This cell line will target tissue repair and recovery in ischemic white disease/vascular dementia, a chronically progressive and dementing condition with no current therapy.
Major Proposed Activities (as written by the applicant)	• Efficacy. 1) Determine most efficacious iPS-GEP line; 2) Test efficacy in chronic white matter stroke; 3) Test efficacy for transplant location; 4) Test dose response; 5) Test efficacy in aged mice • Mechanism of Action. 1) Determine cell intrinsic vs extrinsic effects; 2) Identify expression profile of iPS-GEPs during tissue repair; 3) Identify molecular systems that produce recovery of function • Assay Development.: 1) Qualify identity, purity, safety and stability assays for iPS-GEPs • Biomarker Development. 1) Develop structural MRI biomarker of iPS-GEP repair of damaged white matter; 2) Develop resting state MRI biomarker of enhanced brain connectivity
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	$2,096,095
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

Scoring Data

Final Score: 89

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

Mean	88
Median	89
Standard Deviation	2
Highest	90
Lowest	85
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	14
(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 the necessary significance and potential for impact?	13	0	0
Is the rationale sound?	11	1	0
Is the proposal well planned and designed?	13	0	0
Is the proposal feasible?	13	0	0

Reviewer Comments

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

Strengths

- The use of restricted glial progenitor cells is an attractive approach to treating stroke-related damage
- Transplantation several days after injury is a very attractive feature of this work, and the proposal to also conduct studies in 18-month animals is a very important set of experiments that is far too often neglected
- Stroke is a vital subject area for funding translational research
- Highly translational set of experiments noted, with focus on making available a set of clinical grade glial progenitor cells for white matter injury
- The development of non-invasive imaging biomarkers is a very positive aspect to this work
- Using 18 months old animals (unbiased repair potential)
- project plan is well conceived, detailed, and documented
- Track record of PI in the field of stroke was highlighted
- The PI has two prior CIRM awards; completed 2/2 milestones on one, and 4/4 milestones on another

Concerns

- Analysis of mechanism on a factor-by-factor basis is seen as a minor priority due to the multiple contributions of glial cells to support other cells in the neural environment
- It would be valuable to provide a more detailed analysis of the types of astrocytes being generated, using both the Sofroniew and Barres classification systems
- Not characterizing the astrocytes
- Biomarker development noted as add-on and may deviate from the theme of assessing the therapeutic value of glial progenitor cells
- Despite completing milestones on previous proposals, no publications; if 6/6 milestones have been accomplished, surely at least one merits a publication
- No publications from previous awards

DISCOVERY

Application #	DISC2-10604
Title (as written by the applicant)	Stimulating endogenous muscle stem cells to counter muscle atrophy
Research Objective (as written by the applicant)	Intramuscular delivery of two repurposed FDA approved drugs will activate resident muscle stem cells. This therapeutic strategy will augment regeneration and restore strength to atrophied muscles.
Impact (as written by the applicant)	Currently effective treatments are lacking for localized muscle atrophy due to nerve injury (eg., Carpal Tunnel Syndrome) or immobilization after trauma or surgery (eg., hip or knee replacement).
Major Proposed Activities (as written by the applicant)	• To establish the optimal dose of the formulation based on the stem cell proliferative response and safety profile • To establish biomarkers for efficacy of the formulation in muscle regeneration • To establish the non-invasive biometrics for functional outcome of intramuscular treatment • To assess long-term effects of drug treatment on aged muscle regeneration • To address regenerative response of the drug treatment in aged denervation muscle atrophy model • To evaluate the efficacy of the drug treatment on human muscle xenograft
Statement of Benefit to California (as written by the applicant)	Our therapeutic strategy stands to revolutionize treatment of muscle atrophy. Muscle wasting is a highly debilitating condition that impacts quality of life and productivity with an incidence that increases with aging. In particular, Carpal Tunnel Syndrome, a work related injury, impedes use of the hand with economic consequences. As California is the most populous state, with an ever-increasing elderly population, it will benefit from strategies that increase mobility of this demographic.
Funds Requested	$2,198,687
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

Scoring Data

Final Score: 88

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

Mean	87
Median	88
Standard Deviation	5
Highest	90
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	1

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have the necessary significance and potential for impact?	14	0	0
Is the rationale sound?	12	1	1
Is the proposal well planned and designed?	9	3	2
Is the proposal feasible?	9	0	5

Reviewer Comments

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

Strengths

- The novelty of the drug combination is intriguing
- Simple straightforward approach with two clinically approved drugs; potentially impactful
- Interesting strategy
- Goal is improving recovery of muscle function after denervation; this is an important and unsolved problem
- Drug treatment in vitro of stem cells and in vivo demonstrate an increase in muscle stem cell number
- The luciferase model for testing the concept is good
- Simple design is feasible
- Task to explore safety and efficacy is straightforward
- Great team

Concerns

- Preliminary data is limited
- Would have been easy to accumulate preliminary data to support the application
- More data on the level of drug in situ would be useful
- More data on the in vivo response to the drug combination would be useful
- Half-life appears to be on the order of seconds (after intravenous Injection); not clear if this will enable muscle regeneration
- Very short half-life - it is unclear if it is enough to have an effect
- Drug combo has never been co-injected; never been injected intramuscularly

DISCOVERY

Application #	DISC2-10753
Title (as written by the applicant)	Generation and in vitro profiling of neural stem cell lines to predict in vivo efficacy for chronic cervical spinal cord injury.
Research Objective (as written by the applicant)	This project generates new cGMP compliant tissue educated human neural stem cell lines, paired with in vivo pre-clinical proof of concept testing, and development of a predictive in vitro profile.
Impact (as written by the applicant)	Identification of new cell lines with in vivo efficacy testing to enable efficient translation to chronic cervical spinal cord injury, an area of significant unmet medical need.
Major Proposed Activities (as written by the applicant)	• Derivation of new human neural stem cell lines • In vitro characterization of human neural stem cell lines • Construction of an in vitro cell line profile that can discriminate in vivo efficacy potential • In vivo analysis of human neural stem cell line efficacy after transplantation into spinal cord injured mice
Statement of Benefit to California (as written by the applicant)	The impact of this research includes generation of new CD133-enriched tissue-educated cGMP compliant human neural stem cell lines, which have demonstrated capacity for translation into the clinical for multiple neurological disorders, and development of a profile that can relate in vitro expression analyses from these cells under growth and differentiation conditions to in vivo efficacy. Both of these are critical steps for effective translation.
Funds Requested	$1,575,613
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

Scoring Data

Final Score: 85

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

Mean	86
Median	85
Standard Deviation	6
Highest	95
Lowest	75
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	11
(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 the necessary significance and potential for impact?	12	2	1
Is the rationale sound?	13	1	1
Is the proposal well planned and designed?	12	1	2
Is the proposal feasible?	11	1	3

Reviewer Comments

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

Strengths

- Treatments for cervical SCI are badly needed, and this is one of the top teams to study the utility of NSC transplantation for such purposes
- Strong preliminary data
- The team has already shown their ability to identify and study in detail different NSC populations that differ greatly in their efficacy in SCI transplants
- Rigorous design
- The enormous care taken in cell characterization is exactly what is needed in the field of stem cell medicine, and it is rare to see an application with such attention to the detail of cell generation and characterization
- Beautiful cell line

Concerns

- The grant is poorly structured in terms of presenting the in vivo experiments to be conducted, leading to confusion about how the cells will be evaluated for their functional activity
- A concern with the proposal is that little in vivo validation of the cell lines is proposed
- The proposal will generate a reagent but does not propose to use the reagent (cell line) in experiments
- Not translational - won't make it to the clinic in a reasonable amount of time

DISCOVERY

Application #	DISC2-10751
Title (as written by the applicant)	Silicon Nanopore Membrane encapsulated enriched-Beta Clusters for Type 1 Diabetes treatment
Research Objective (as written by the applicant)	We propose to develop a cell encapsulation technology to support the long term viability and function of human stem cell derived insulin producing cells.
Impact (as written by the applicant)	A device that provides adequate mass transfer of oxygen, glucose, and insulin for encapsulated stem cell derived beta cells can address the challenges of current cell therapy for Type 1 Diabetics.
Major Proposed Activities (as written by the applicant)	• Generate and model various Cell Scaffold designs to house stem cell derived beta cells. • Fabricate and characterize the Cell Scaffold in vitro to determine stem cell derived beta cell functionality. • Evaluate various iBAP prototypes for proper fit within the tissue pocket. • Prototype and evaluate iBAP vascular connections after implantation. • Determine the dose of beta cells for glucose autoregulation in the diabetic model. • Demonstrate chronic glucose autoregulation in vivo in the diabetic model.
Statement of Benefit to California (as written by the applicant)	Type 1 Diabetes affects over 250,000 Californians. A device encapsulating stem cell derived beta cells represents a functional cure for Type 1 Diabetes patients. However the poor transport of oxygen, glucose, and insulin of previously developed devices severely limits these device's clinical potential. We will develop an encapsulation technology that solves these mass transfer problems, provides physiologic glucose control, and achieves the first functional cure for Type 1 Diabetes.
Funds Requested	$1,113,000
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

Scoring Data

Final Score: 85

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

Mean	85
Median	85
Standard Deviation	2
Highest	90
Lowest	81
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	13
(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 the necessary significance and potential for impact?	12	0	2
Is the rationale sound?	9	3	2
Is the proposal well planned and designed?	11	1	2
Is the proposal feasible?	8	2	4

Reviewer Comments

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

Strengths

- Very innovative approach - different than what others are doing
- The novel approach proposed has a chance of being better than the encapsulation approaches used by others and is therefore significant and important; in spite of the recent attention that has been focused on encapsulation as an approach that could protect transplanted beta cells from transplant rejection and autoimmunity, there are major challenges facing both micro- and macro-encapsulation
- Very relevant to the stem cell field because transplantation of stem cell-derived beta cells will require a delivery device
- Device design and engineering is supported by strong preliminary data
- Device design has been conducted in a superb manner; in vitro data support functionality of islets in the device (Fig.12), beneficial effects of inducing convective flow (Fig. 11) and exclusion of inflammatory cytokines (Fig. 6)
- There is evidence that flow path through the device was patent throughout 26 days of the implant without the need of systemic anticoagulants
- Only team in the world with the expertise to undertake it

Concerns

- One of the big questions that needs to be addressed is how much permselectivity will be required to provide immune protection; some hypothesize that it is only necessary to exclude cells and that excluding cytokines is a non-issue
- Progress has also been made in generating beta-like cells from embryonic stem cells, although it is unclear as to what is meant by generating “mature beta cells 92% identical to native human beta cells”
- A big issue for packing density is the purity of beta cells; it is unclear what percentage of the cells are non-hormone-secreting cells
- Figure 4 shows some excellent initial data, however, there does not appear to be any functional data following transplant to suggest that these cells can support a diabetic animal
- No in vivo data are provided to support functionality of the device and no in vivo data to support functionality of stem cell-derived beta cells
- Consideration of intimal hyperplasia on anastomoses as found in dialysis grafts is of concern and will likely impact long-term sustainability
- Biofouling/capsule formation of device may impact long term sustainability

DISCOVERY

Application #	DISC2-10695
Title (as written by the applicant)	Identification and Generation of Long Term Repopulating Human Muscle Stem Cells from Human Pluripotent Stem Cells
Research Objective (as written by the applicant)	We will molecularly and functionally define muscle stem cells in human muscle in development, juvenile and adult and develop strategies to generate the most regenerative muscle stem cells from hPSCs.
Impact (as written by the applicant)	There is no clinically relevant cell endowed with continuous repopulation ability from hPSCs. This work could provide a cell therapy for muscle disorders including muscular dystrophies or sarcopenia.
Major Proposed Activities (as written by the applicant)	• We will perform single cell RNA sequencing (scRNA-seq) of embryonic, fetal, juvenile and adult muscle stem cells (MuSCs) and identify unique gene signatures and cell states across human myogenesis. • We will identify unique cell surface markers on in vivo derived MuSCs that distinguish PAX7-positive cells from other muscle cells and across cell states. • Evaluate myogenic ability and functional differences of embryonic, fetal, juvenile and adult MuSCs in fusion, proliferation, engraftment and repopulation assays in mouse models of muscle disease. • Develop transcription factor over-expression in combination with improved directed differentiation strategies to generate MuSCs from hPSCs with genetic and functional signatures of the in vivo MuSCs. • Demonstrate ability to expand optimal MuSC population from hPSCs for 3-6 passages using novel small moleules without loss of engraftment and repopulation potential in mouse models of muscle disease. • Identification of one translational candidate MuSC population from hPSCs capable of continuous repopulation after injury.
Statement of Benefit to California (as written by the applicant)	A large majority of California residents are affected or will be affected with a muscle disease in their lifetime including severe muscular dystrophies, aging related muscle loss called sarcopenia or muscle weakness. The research in this propoal will benefit CA residents tremendously by understanding how to generate a muscle stem cell capable of responding to injury and undergoing long term repopulation after injury to generate new muscle. Funding will also support additional staff in the lab.
Funds Requested	$2,184,000
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

Scoring Data

Final Score: 85

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

Mean	84
Median	85
Standard Deviation	3
Highest	90
Lowest	80
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	11
(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 the necessary significance and potential for impact?	13	0	1
Is the rationale sound?	11	0	3
Is the proposal well planned and designed?	10	1	3
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

- Use of embryonic stems cells in an application where iPS cells do not work as well
- Mapping at high resolution all cell types should provide a generally useful data set
- Very convincing preliminary data
- Strong proposal from strong investigator

Concerns

- Full analysis plan for resulting data is a little vague; more hypotheses should be articulated, with specific analytical plans described
- No milestones yet completed from previously awarded CIRM grants

DISCOVERY

Application #	DISC2-10747
Title (as written by the applicant)	Targeting Cancer Stem Cells in Hematologic Malignancies
Research Objective (as written by the applicant)	We will develop a biotherapeutic/monoclonal antibody that blocks the growth of human AML cancer stem cells in vitro and in vivo.
Impact (as written by the applicant)	Treatment of the cancer stem cell driven disease Acute Myelogenous Leukemia (AML) will be impacted. AML is the most common acute leukemia in adults and current treatments are largely ineffective.
Major Proposed Activities (as written by the applicant)	• Development of monoclonal antibodies • Identification of monoclonal antibodies that can block human AML growth in vitro • Optimization of dose and delivery of monoclonal antibodies in vivo • Identification of monoclonal antibodies that can block human AML growth in vivo • Define impact of monoclonal antibodies on cancer stem cells in vivo by high resolution imaging
Statement of Benefit to California (as written by the applicant)	Because this research will lead to the development of new treatments for the deadly disease acute myelogenous leukemia, the State of California and its citizens will directly benefit. While AML is the most common adult leukemia, it also accounts for more than 50% of all leukemia-associated mortality in children. Thus, if successful, the biotherapeutic we propose to develop would improve outcomes for patients across a broad range of ages throughout the State of California
Funds Requested	$2,167,200
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

Scoring Data

Final Score: 85

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

Mean	84
Median	85
Standard Deviation	3
Highest	87
Lowest	75
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	12
(1-84): Not recommended for funding	3

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have the necessary significance and potential for impact?	13	0	1
Is the rationale sound?	10	2	2
Is the proposal well planned and designed?	7	1	6

Is the proposal feasible?	10	1	3

Reviewer Comments

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

Strengths

- Novel therapeutic approach to AML
- Under-explored area with high relevance to cancer/stem cells
- Good preliminary data
- The proposed work benefits from a large and convincing set of preliminary evidence suggesting that the target gene could affect the leukemia growth or maintenance; as such, the work is well supported by a strong rationale
- The project has ample and convincing preliminary results showing that interfering with the target gene can impact on the AML incidence in mouse models; the notion that blast crisis progression of chronic myeloid leukemia cells is associated with target gene expression further extends the applicability of the proposed therapy
- Straightforward research plan
- The proposed work has a clear vision for progression from discovery of a new mAb to its testing to preclinical work to eventual translation
- The proposed work is well laid out, and the use of both in vitro colony assay formation, CXCR4 response inhibition, in vivo work, including xenograft in vivo work, are well justified

Concerns

- Induction of antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity is a concern
- More extensive toxicity studies should be planned
- The PI is encouraged to provide a deeper consideration to potential toxicity in mice treated with the mAb
- Ab mediated toxicity is a concern; eg. to central nervous system; could be a potential drawback to ultimate therapeutic use
- More basic biology of the target would be nice as preliminary data
    - Literature and data mining to see if there is additional support of the interaction of the two genes
    - Evolutionary conservation studies to determine how far back in the evolutionary tree clear orthologs of these two genes can be identified
- The approach taken does not directly make us of stem cells or stem cell technology, rather it tackles the notion that leukemia is driven by a cancer stem cell and the proposed work would target a surface marker with a yet to be generated monoclonal antibody mAb
- It is not clear there is use of stem cells in this proposal; the invocation of CSCs in later aims seems unnecessary and merely included to intersect with the scope of stem cells
- The project has development plan that is well justified, however, it totally depends on the success of aim 1, since without a mAb candidate none of the validation work can be carried out
- If cannot make a mAb, proposal will be dead in the water before getting to Milestone 2
- Personnel roles are too vague: e.g. "He will be involved in all aspects of the work;" "He will contribute significantly to the scientific execution of the work and will be responsible for carrying out many of the proposed studies."

DISCOVERY

Application #	DISC2-10559
Title (as written by the applicant)	Development of immune invisible beta cells as a cell therapy for type 1 diabetes through genetic modification of hESCs
Research Objective (as written by the applicant)	Development of hESC-derived pancreatic beta cells that are protected from allogeneic and autoimmune attack into a cell therapy for type 1 diabetes (T1D)
Impact (as written by the applicant)	Cell therapy of T1D is challenged by immune rejection. Therefore, we will develop pancreatic progenitors derived from genetically modified hESCs that can evade allogeneic and autoimmune responses.
Major Proposed Activities (as written by the applicant)	• To differentiate genetically modified hESCs into pancreatic β-cell precursors that express two immune suppressive molecules CTLA4-Ig and PD-L1. • To reconstitute immunodeficient mice with human immune system, denoted Hu-mice. • To test whether CTLA4-Ig/PD-L1(CP)-expressing pancreatic β-cell precursors derived from hESCs can evade immune responses to foreign cells. • To develop humanized autoimmune T1D model reconstituted with pancreatic beta cells and autoimmune human immune system from the same individual. • To validate that CP-expressing pancreatic β-cells can evade autoimmune responses in T1D autoimmune model. • To test whether CP-expressing pancreatic β-cells derived from hESCs can reverse insulin dependence in humanized T1D autoimmune model.
Statement of Benefit to California (as written by the applicant)	This proposal aims to find a cure for diabetes, which affects 2.3 million Californians and is associated with medical expenditures 2.3 times higher than in people without diabetes. An ultimate treatment for diabetes would be to transplant lost insulin-producing beta cells without need for immunosuppression therapy. This proposal will generate and test non-immunogenic beta cells derived from human embryonic stem cells as a renewable source of transplantable insulin-producing beta cells.
Funds Requested	$2,167,200
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

Scoring Data

Final Score: 85

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

Mean	83
Median	85
Standard Deviation	5
Highest	90
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	11
(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 the necessary significance and potential for impact?	13	0	2
Is the rationale sound?	10	3	2
Is the proposal well planned and designed?	9	2	4
Is the proposal feasible?	9	4	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 rationale is sound, the beta cell supply problem may be on its way to being solved but autoimmunity and allorejection remain a serious challenge; much work is being done with encapsulation but it is not clear how much success can be achieved; in the end the goal is to be able to transplant naked islet cells and gene engineering is an attractive approach that needs to be pursued
- The overall proposed work is well justified by recently published work; the expression of CTLA4-Ig and PD-L1 by hESCs appears to provide a strong immune-evading outcome
- The proposed work is well supported by strong preliminary results showing the generation of humanized mouse models capable of mounting anti-allograft responses in vivo
- Robust humanized mouse and immunological approaches to test the hypothesis
- Both aims are well constructed and will yield important findings; the PI considers a previously graft-rejected mouse model to test for tolerance in a primed host
- Excellent team to undertake immunological studies
- Team of experts in stem cell biology and transplantation immunology
- The research team has ample expertise in the differentiation of hESC into beta-cells

Concerns

- The concern that the CTLA4-Ig expressing cells could lead to generalized immune-suppression in the recipient was diminished by the recent reports, however, the proposed work should still directly address whether functional immunity to a viral challenge, or the like, is not compromised in mice with CP-hESC-derived cells
- While the proposed experiments should be done, it is not clear that these two manipulations will be sufficient to provide full protection
- CTLA4-Ig and PD-L1 may not be sufficient to solve the problem
- Approach of CTLA4-Ig and PD-L1 may not be sufficient to counteract
- Lack of functional data on beta cells
- There are no data to provide evidence that ES-derived beta cells are functional (e.g., glucose-stimulated insulin secretion, perifusion, diabetes reversal after transplantation in mice); data provided in Fig. 3 show characterization of of cell expression by IHC and FACS
- Cells are only characterized phenotypically not functionally
- The mouse models will be a useful way to test these cells but the humanized mice are not yet at the point where they truly mimic what will occur in a real human transplant situation, the autoimmune model that is being developed could turn out to be useful
- Humanized mouse model may not be developed enough to test their hypothesis

- ES rejection in Hu-mice is not very efficient (Fig. 2E); this is not a very good model to test immunoprotection of allografts
- Model to assess immune responses is teratoma - a strong effect is not demonstrated
- Different sites (subcutaneous and kidney capsule) are proposed to evaluate immunogenicity and functionality of CP-beta cells from ES; differentiation and immunogenicity may be affected by the site so there should be consistency in the site chosen for testing
- Subcutaneous sites and kidney capsule sites add variability to immune responses
- Although aim 2 directly considers an autoimmune response generated against a model neo-antigen, a more straightforward set of antigens like insulin or IGRP could have been considered and used to prime mice prior to transplanting the CP-hESC-derived beta cells
- Beta cells derived from iPSCs may be immunogeneic even in the context of autologous transplant, so there may be no need in expressing the neo-antigen in them
- References cited for islet transplantation are very old; Figures (5) and panels (Fig. 1C,D) cited within the text are missing

DISCOVERY

Application #	DISC2-10599
Title (as written by the applicant)	Translational Imaging Tools for Human Regenerative Therapies
Research Objective (as written by the applicant)	This proposal will provide new ways to overcome roadblocks to sensitive in vivo imaging methods that can monitor the fate of transplanted stem/progenitor cells for a range of human disease conditions.
Impact (as written by the applicant)	Total-body positron emission tomography (PET) with unprecedented sensitivity to detect and monitor small quantities of cells is needed to ensure the safety of cell therapies proposed for humans.
Major Proposed Activities (as written by the applicant)	• Create three-dimensional simulated organs with different quantities and types of human stem/progenitor cells and different shapes and sizes. • Synthesize a stem cell label and test to ensure that the labeling technique does not alter the viability or function of the cells after labeling. • Compare transformative total-body PET imaging to current human clinical PET scanners to simulate in vivo conditions and select cell doses to be tested for in vivo imaging. • Identify cell doses for transplantation and test in preclinical models that simulate young humans (infants and children). • Develop efficient techniques for the detection and quantification of human stem cells for transplantation in patients for regeneration and repair and methods to monitor cell fate and safety over time. • Initiate the process for translational applications to human subjects in need of new methods to monitor transplant outcomes safely and noninvasively.
Statement of Benefit to California (as written by the applicant)	This transformative PET imaging technology will benefit the State of California and citizens of all ages across the lifespan. Once highly sensitive and quantitative imaging techniques are developed that can accurately and safely monitor transplanted cells over time, this will provide a powerful tool to determine the long-term fate of stem cells after administration to patients. The results of these studies will fill a critical need and substantially advance the regenerative medicine field.
Funds Requested	$1,100,400
GWG Recommendation	***(1-84): 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 median of the individual member scores. Additional parameters related to the score are shown below.

Mean	83
Median	84
Standard Deviation	2
Highest	85
Lowest	80
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	7
(1-84): Not recommended for funding	8

Score Influences

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

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have the necessary significance and potential for impact?	11	1	2
Is the rationale sound?	10	1	3
Is the proposal well planned and designed?	5	5	4
Is the proposal feasible?	8	3	3

Reviewer Comments

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

Strengths

- Outstanding technology
- Plenty of data are provided to demonstrate feasibility of proposed studies using both PET and bioluminescence, improved radioimmuneconjugates, assays for determining retention and toxicity of probes in stem cells, sensitivity of their tool
- Wide breadth of stem cells and progenitors measured
- The team is currently developing a PET scanner for clinical use
- Outstanding PI and team

Concerns

- Conditions to be tested in animal models are not clear for the minimal number of animals requested (male and female, four different cell types, different cell doses)
- It is unclear how the number of cells will be titrated with n=4 animals per sex if doses of 10 to 10^6 will be achieved; ie. if one animal will receive more than one scaffold
- It is unclear if scaffolds will be retained for 30 days to enable a stable microenvironment for cell number measurement
- Choice of using different scaffold types won't allow titrating the resolution per cell types; concern the cells migrate away
- Transplantation of human cells in large animal studies with monitoring up to 4 weeks after transplantation without any immunosuppression may not be feasible; preliminary data showing survival and detection by PET of human cells in the large animal models up to 4 weeks are needed
- Small animal models may be more relevant to gauge cell number range since 10 to 10^6 cells appears to be a large range to study in a low number of large animals
- No preliminary data are provided for in vitro assays for post-labeling assessments of radio labeling
- In figure 7, 25 x 10^6 cells were injected but it is not clear what number (or range) of cells is detected

DISCOVERY

Application #	DISC2-10665
Title (as written by the applicant)	Neural Stem Cell Relays for Severe Spinal Cord Injury
Research Objective (as written by the applicant)	We propose to utilize human neural stem cells to form neuronal relays across sites of severe SCI, restoring function across the site of spinal cord injury.
Impact (as written by the applicant)	We will develop a specific type of neural stem cell that is best suited for repairing the injured spinal cord.
Major Proposed Activities (as written by the applicant)	• In Vitro Assessment of GMP-compatible H9-scNSC Batches. • In Vivo Assessment of GMP-compatible H9-scNSC Batches. • In Vivo Assessment of Disease Modifying Activity over time, Model 1: T10 moderate contusion. • In Vivo Assessment of Disease Modifying Activity over time, Model 2: T3 severe compression. • In Vivo Assessment of Disease Modifying Activity over time, Model 1: C5 moderate contusion. • FDA Pre-pre IND Meeting.
Statement of Benefit to California (as written by the applicant)	Spinal cord injury (SCI) affects approximately 300,000 people in the U.S., with more than 11,000 new injuries per year. This research plan will examine a novel therapeutic strategy for SCI. Neural stem cells will be generated from human embryonic stem cells and grafted into animal models of SCI. We predict neuronal relays will form across a SCI lesion site that will mediate behavioral recovery. These studies will form the basis for clinical translation for the treatment of spinal cord injury.
Funds Requested	$2,100,581
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 80

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

Mean	82
Median	80
Standard Deviation	3
Highest	90
Lowest	80
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	5
(1-84): Not recommended for funding	10

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have the necessary significance and potential for impact?	11	1	2
Is the rationale sound?	7	4	3

Is the proposal well planned and designed?	8	5	1
Is the proposal feasible?	6	3	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

- Huge, unmet need in this area
- Successful therapy would be incredible
- Clear path to translation
- High impact
- Strong preliminary data
- Multiple animal models
- Excellent laboratory
- Strong team and environment

Concerns

- The basic premise of establishing a relay is an untested assumption; if the transplanted cells are promoting growth of host cells, and it is the host cells that are responsible for behavioral improvement, then a transection post-transplantation would have exactly the same effects (along with the damage caused by the transection)
- The idea of organized information transmission is lacking in support; at the site of transplantation, there is chaos rather than organization
- Data that indicates that there is a topologically meaningful relay of information is needed; this is particularly a concern as the recovery is not large, and remains within the range that might be obtained by restoring function of a local pattern generator
- Given the relatively small improvement in experiments with tightly controlled variables, the odds of this translating in a verifiable manner to the highly variable situation of human injury are low; it is unclear whether one could analyze enough patients to figure out if this works
- Fig. 9 is confusing, it is expected that control would improve over time; it is unclear how to make sense of the experimental animals in the context of the control
- Fig. 9 shows minimal improvement - it is unclear how many patients will be needed to show therapeutic efficacy
- Milestones 3-5 are the same experiment using different damage models it may be better to show that the cells work in one model before moving on
- Complex therapy (matrix, cells, growth factors) for clinical translation
- There is no discussion of the multi-component transplant they propose with multiple growth factors, a matrix and cells; with such a complex transplant, it would be helpful to initiate discussions already with FDA to determine whether this approach would even be allowed for an IND
- The age of the animals transplanted is not provided; If these are young animals (as they usually are) then they may give very different outcomes than would occur in an older animal; yet, it is the one year old rat that is the age equivalent of the 30 year old human that is closer to (but still below) the median age group for SCI
- Age of animals in experimental plan is missing
- Pharmacokinetics of growth factors in graft not assessed

DISCOVERY

Application #	DISC2-10647
Title (as written by the applicant)	Development of PEG-PTN for Hematopoietic Regeneration
Research Objective (as written by the applicant)	We will develop a stable form of a hematopoietic stem cell growth factor for clinical application.
Impact (as written by the applicant)	Hematopoietic recovery will be improved in myelosuppressed chemotherapy patients.
Major Proposed Activities (as written by the applicant)	• Generation and validation of PEGylated growth factor. • Complete pharmacokinetic analysis of PEGylated growth factor. • Demonstrate effectiveness of PEGylated growth factor in radiation injury model. • Demonstrate effectiveness of PEGylated growth factor in bone marrow transplant model. • Demonstrate effectiveness of PEGylated growth factor in chemotherapy model. • Conduct murine toxicology studies to determine the potential for human drug toxicity and adverse effects.
Statement of Benefit to California (as written by the applicant)	A common life threatening side effect of chemotherapy is neutropenia accompanied by fever or febrile neutropenia. Patient morbidity, recovery time, and hospitalization in the patient population could be reduced by the addition of our candidate drug to standard treatment regimens.
Funds Requested	$960,380
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 80

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

Mean	81
Median	80
Standard Deviation	7
Highest	90
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	7
(1-84): Not recommended for funding	8

Score Influences

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

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

Reviewer Comments

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

Strengths

- There is a need for more hematopoietic stem cell (HSC) boosters for bone marrow stresses
- New agent with potential impact on HSC
- Innovative compound
- Preliminary data are strong especially published data
- Has responded to prior reviews with new PEG-PTN that is more potent
- Excellent preliminary reports that are peer reviewed
- Well-written proposal
- The PI has obtained important commitment of support from their institution

Concerns

- There are currently two well-characterized compounds that can effectively and robustly expand HSCs, SR1 and UM171, both currently undergoing clinical trials, which have superior activity as shown in pre-clinical results, which makes PEG-PTN a less attractive avenue of investigation
- There are other HSC stimulants in the pipeline that were not discussed
- Potential for improvement may not be substantively better than G-CSF alone, however there is synergy with G-CSF
- It is unclear whether the compound is better than G-CSF when used as monotherapy and whether it is going to be effective in radiation injury
- Concern regarding reactivation of minimal residual disease in leukemia for transplant; while it may be outside the scope of the proposal, it is not discussed
- Potential pitfalls and alternative approaches are discussed; in particular as it pertains to the expected results of milestone 1, the PI considers some issues related to the valency of the PEG-PTN product; however, it is curious that the PI has not considered an Fc-fusion set up to also increase in vivo availability of PTN, while also increasing its valency
- Radiobiology approach is studied in sublethal doses with survival demonstrated in untreated controls; it is unclear what happens at 1000cGy
- The project milestones follow a logical timeline, however, milestone 1 appears to represent a make or break step in the project
- Other ways to stabilize PTN were not considered
- Future human experiments were not detailed at all
- Poor support for PI

DISCOVERY

Application #	DISC2-10433
Title (as written by the applicant)	Development of a new therapeutic for directing target specific stem cell migration and treatment
Research Objective (as written by the applicant)	A drug-stem cell combination therapy wherein the drug will direct and promote the delivery and distribution of stem cells to the disease site for the optimal therapeutic effect of the stem cells
Impact (as written by the applicant)	Amyotrophic lateral sclerosis (ALS) and the way to deliver and enhance stem cell-based treatment of ALS
Major Proposed Activities (as written by the applicant)	• Complete the additional in vitro studies and initiate the in vivo studies in SOD1 mouse model • Determine whether the combined effect of hNSCs intraspinally augmented & guided by SDV1a has a synergistic effect on improving disease onset/progression & symptom-free survival in the SOD1 mouse • Establish the preliminary toxicity and pharmacokinetics profiles of SDV1a in mouse model • Elucidation of structure and other characteristics; Development and validation of analytical procedures • Process development and characterization in lab scale, stability study
Statement of Benefit to California (as written by the applicant)	This new therapeutic will address a significant unmet medical need in the treatment of amyotrophic lateral sclerosis (ALS) and have important benefits to the patients with ALS and impact on the healthcare and bio industry in California.
Funds Requested	$1,906,900
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 80

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

Mean	80
Median	80
Standard Deviation	2
Highest	82
Lowest	75
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have the necessary significance and potential for impact?	11	0	2
Is the rationale sound?	8	2	3

Is the proposal well planned and designed?	3	2	8
Is the proposal feasible?	3	3	7

Reviewer Comments

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

Strengths

- ALS is a lethal disease for which there is no cure or effective therapy
- The novel drug-stem cell combination therapy proposed in this application is built on recent advances in the field
- The use of SDV1a in combination with NSC could have potential in enhancing a cure for ALS patients
- Rationale is logical and may lead to a therapeutic
- The investigators present strong preliminary data on 1) design, synthesis and receptor binding ability of SDV1a; 2) SDV1a triggered migration of NSC both in vitro and in vivo; 3) biodistribution of SDV1a in animal brains; and 4) the therapeutic benefits of the co-injection of SDV1a and NSC in vivo
- SDV1a seems mature and well-studied from a structure and mechanism of action point-of-view
- The primary investigator has a long and proven record of working with many leading biologists and clinicians to advance new therapeutics toward clinical applications
- Co-investigator is an expert in stem cell biology who has conducted extensive research and development of human neural stem cells for the clinical applications in ALS and other neurologic diseases
- Investigators have worked together especially in the biological and translational studies of neural stem cells
- The pitfalls overall are well thought out and presented
- Good translational potential

Concerns

- Key data on different routes of administration are not described
- A plan and vision for route of administration in humans for SDv1a is needed
    - Much of the preliminary data shows direct injection at site of injury but other text seems to imply general infusion
    - It is unclear whether infusion away from injured site will work at all, or as well as site-targeted delivery
- It is unclear whether the proposed studies will be able to differentiate the effects (if any) of exogenous vs endogenous stem cells
- Did not respond to previous concern about lack of publications from earlier proposal; stating that a paper is submitted is insufficient
- Some concerns raised by the previous review were not addressed

DISCOVERY

Application #	DISC2-10626
Title (as written by the applicant)	Develop iPSC-derived microglia to treat progranulin deficient Frontotemporal Dementia
Research Objective (as written by the applicant)	Develop stem cell-based therapy to treat dementia
Impact (as written by the applicant)	There are no treatments for dementia. If successfully achieved, this study will lead to a cure of a familial form of dementia in the elderly population.
Major Proposed Activities (as written by the applicant)	• Develop a robust human stem cell-derived microglial platform for cell-based therapy • Determine short-term safety and efficacy of engrafted human microglia in wildtype mice • Determine short-term efficacy of engrafted human microglia in Frontotemporal Dementia (FTD) mouse models • Determine long-term efficacy of engrafted human microglia in FTD mouse models
Statement of Benefit to California (as written by the applicant)	The proposed research will benefit the State of California and its citizens because of the potential to cure a major form of dementia in the elderly population. With the fast aging population in California, more and more Californians are diagnosed with neurodegenerative dementias. There is an urgent need to develop a treatment or cure for these devastating conditions. Success of our study will address this urgent medical challenge of our modern society.
Funds Requested	$1,929,714
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 80

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

Mean	80
Median	80
Standard Deviation	3
Highest	85
Lowest	75
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	3
(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 the necessary significance and potential for impact?	9	1	2
Is the rationale sound?	8	2	2
Is the proposal well planned and designed?	5	2	5

Is the proposal feasible?	5	3	4

Reviewer Comments

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

Strengths

- Important unmet medical need
- Novel therapeutic approach
- Outstanding preliminary data
- Translational potential

Concerns

- Long-term immunosuppression in model was a concern
- It is uncertain whether sufficient microglia can be generated
- There are concerns about the number of cells that can be generated
- There are concerns about phenotype of microglia before and after transplantation - how to distinguish between donor and host cells

DISCOVERY

Application #	DISC2-10525
Title (as written by the applicant)	Development of a Cellular Therapeutic for Treatment of Epilepsy
Research Objective (as written by the applicant)	A stem cell-derived nerve cell therapy to minimize seizures in people with epilepsy
Impact (as written by the applicant)	Many people with epilepsy have uncontrolled seizures that can be life threatening and adversely impact quality of life and independence. A cell therapy could help those not responsive to drugs.
Major Proposed Activities (as written by the applicant)	• Transplant a nerve cell therapy made with clinically compatible methods into a mouse model of epilepsy to reduce seizures and understand how the cells function in the brain • Transplant a nerve cell therapy made with clinically compatible methods into a rat model of epilepsy to reduce seizures and understand how the cells function in the brain • Work to cryopreserve the nerve cells and see if they are the same in a dish before and after freezing • Transplant the cryopreserved nerve cells into the mouse brain to see if they are the same before and after freezing • Characterize different batches of the nerve cells to show they are the same and then compare with data from transplantation studies to see what cell characteristics are most important for activity • Prepare for a meeting with the FDA to present a well-informed development plan based on the data obtained in Activities 1-5
Statement of Benefit to California (as written by the applicant)	Approximately 370,000 adults in California live with epilepsy. They have spontaneous seizures that are unpredictable, uncontrollable, and very disabling, impacting health and their degree of independence. One-third of people with epilepsy do not respond to anti-epileptic drugs and brain resection is their best treatment option. Better treatments for seizures could improve the quality of life for people living with the chronic disease and decrease the lost wages and productivity to California.
Funds Requested	$1,616,536
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 80

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

Mean	78
Median	80
Standard Deviation	9
Highest	90
Lowest	60
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	7
(1-84): Not recommended for funding	8

Score Influences

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

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

Reviewer Comments

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

Strengths

- Significant clinical need
- Developing treatments for epilepsy is of great importance, and the possibility of using transplantation of the proposed nerve cells is intriguing
- Huge potential impact as epilepsy has massive morbidity; dirty drugs; many folks not aided by these drugs; even those that are aided might benefit from adjunct (or concomitant therapies such as stem cell therapies)
- Need not show that a novel therapy is better than existing therapies. Need to show that either (1) it has the potential to be better, or (2) that it can occupy a niche that existing therapies do not have (either as an adjuvant/concomitant or part of integrative - or in folks not reached by existing)
- Strong preliminary data
- 98% purity of harvested GABAergic inhibitory neurons from hES cells supported by preliminary data
- Solid preliminary data demonstrating cell survival after transplantation
- Relevant animal models to test safety and efficacy
- The translational potential of this proposal was noted during the review, specifically the introduction of a clinical grade neurons for epilepsy
- PI has a good record with previous CIRM grants, typically achieving some to all milestones and producing numerous publications and IP from these efforts

Concerns

- There are concerns that the neural phenotypes are neither well assessed in the preliminary data nor going to be characterized moving forward
- There is no comparison with established approaches
- Concerns were raised that the description of primary endpoint, i.e., seizures, is too broad, in that animals demonstrating just two seizures per day and a reduction of 30% in seizures after transplantation do not equate to a robust seizure model and therapeutic outcome, respectively
- It is standard practice in this field to use a multi-grade scale to distinguish very different types of seizures from each other, and no such information is provided in this application
- The generation of two seizures per day is impossible to evaluate
    - Seizure events need to be identified, ie. two petit mal type seizures, full blown tonic clonic seizures, etc... as these are very different types of events
    - If these are minor seizures, then generating two per day is unimpressive
    - If they are severe seizures, then there should be a distribution of less severe seizures occurring
- Need to put some effort and detail into describing statistics, ie. power calculations and clear metrics for success
- Doubts about clinically relevant dose and pharmacological action
- There is no discussion of scaling issues, or experiments to address such concerns
- Need to either document existing team's experience in epilepsy or add in another team member with this expertise
- The grant is hard to read from a general structure point-of view
    - To fare better in a review panel, have the proposal vetted by several people outside the immediate field (or perhaps even non-scientists) to make sure they understand and can recapitulate the key points of the proposal

- For example, the details (and summary) of the "therapeutic candidate" are hard to find and understand

DISCOVERY

Application #	DISC2-10546
Title (as written by the applicant)	Exosomes from iPSC-derived cardiomyocytes for porcine model of myocardial injury
Research Objective (as written by the applicant)	Exosomes underlie the mechanism of action of iPSC-derived cardiomyocytes (iCMs). They exhibit pleiotropic effect, contain cytoplasmic miRNAs and proteins, and function as intercellular effectors.
Impact (as written by the applicant)	Exosomes will obviate the major bottlenecks in cardiovascular cell therapy, including ventricular arrhythmia, teratoma, iCM heterogeneity, cell engraftment and electromechanical coupling.
Major Proposed Activities (as written by the applicant)	• Generation of 50 trillion homogenous population of exosomes from the hypoxic iCMs (hEx). • Dose-dependent effect of hEX in restoring the peri-infarct region (PIR) of the injured porcine myocardium. • Exosomes from the hypoxic iCMs (hEXs) will restore both the immuno-competent and -suppressed porcine HF models. • Pre-pre-IND FDA meeting.
Statement of Benefit to California (as written by the applicant)	In California, heart failure is the leading cause of hospital admission; it is a public health epidemic. Despite significant medical advances, the five-year survival remains at a dismal 50%. Clinical promise of the iCMs is obvious, yet, no clear therapeutic strategy has been found. Our published data support the role of the cell-free exosomes released from patient-specific iCMs as the most potent paracrine effector. These autologous exosomes will enable precision medicine for the failing heart.
Funds Requested	$2,180,383
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 78

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

Mean	79
Median	78
Standard Deviation	10
Highest	90
Lowest	55
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	6
(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 the necessary significance and potential for impact?	10	3	0
Is the rationale sound?	6	7	0
Is the proposal well planned and designed?	5	5	3
Is the proposal feasible?	4	5	4

Reviewer Comments

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

Strengths

- The strength of this proposal lies in the potential translational application
- Well-developed study design
- Pig model is a major strength
- Imaging modalities are a strength
- Experienced PI

Concerns

- Concerns about heterogeneity of exosome content and the therapeutic reliability
- Concern regarding the poor characterization of exosome heterogeneity and cargo, for example cargo other than miRNAs
- Consideration of other payloads other than RNA can confound results
- Need to address the possibility that the size of the particles may or may not correspond to cargo
- Concerns have been raised regarding the rationale behind the two animal models used in aims 1 and 2, and a clear mechanistic rationale for whether these exosomes are immunoprivileged or not
- Confusing proposal organization, if the exosomes are immunoprivileged there should be only one Aim (Aim 2)

DISCOVERY

Application #	DISC2-10562
Title (as written by the applicant)	Treating advanced retinal degeneration diseases using a tissue engineered co-graft
Research Objective (as written by the applicant)	The study will look into feasibility of using co-grafts made of human embryonic stem cell derived retina organoids and retinal pigment epithelium to treat advanced retinal degeneration diseases.
Impact (as written by the applicant)	A new cell replacement therapy will be developed for advanced retinal degeneration diseases that are considered to be incurable.
Major Proposed Activities (as written by the applicant)	• Prepare co-grafts made of human embryonic stem cell (hESC) derived retinal pigment epithelium (RPE) and hESC derived retina organoid sheets for making co-grafts. • Find out a suitable adhesion technique to make co-grafts and test it in rats. • Conduct transplantation experiments in retinal degenerate rats to establish the best candidate for efficacy studies. • Conduct implantation surgeries using pig eyes to standardize the procedure for future human clinical trials.
Statement of Benefit to California (as written by the applicant)	The proposed study is aimed to develop a cellular therapy for advanced retinal degeneration (RD) diseases by co-grafting retinal pigment epithelium (RPE) together with retina organoid (RO) sheets. Our preclinical experimentation will seamlessly and quickly transferred into starting clinical trials to develop a novel treatment strategy. Ultimately, hundreds of thousands of Californians with currently incurable RD conditions would benefit from our research.
Funds Requested	$1,883,051
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 78

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

Mean	74
Median	78
Standard Deviation	7
Highest	80
Lowest	60
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

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 the necessary significance and potential for impact?	10	3	2
Is the rationale sound?	4	6	4

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

- Development of innovative tools for deployment of dual product
- Innovative rat model developed to test humanized cells in rats
- Superior outcome measures - electrophysiology, digital histology provides unbiased data
- New testing model will allow generation of more accurate results on visual acuity measures than previously developed models because distance between stimuli and eye will be fixed
- Availability of superior electrophysiology for correlating response area with implant placement
- Rapid incorporation of pig model for translation to clinic
- RPE in clinical trial
- Translation potential: in Milestone 3 they will establish a feasible surgical approach for human clinical trials
- Feasibility of RO established
- Experienced team with excellent track record

Concerns

- The choice of using immunodeficient rats will not allow the team to determine the impact of clinically-relevant immunosuppression on graft integration and function after transplantation
- Immune response in pigs has been described with RPE - consideration of immune responses through analyses of vitreous and histology is recommended
- Preliminary data provided clearly indicated that rosette formation is not prevented even when retinal organoids are transplanted together with polarized RPE sheets; the approach needs to be modified to address this problem they experienced in pilot experiments
- Results from previously funded CIRM grant are not presented; it is unclear how is the approach proposed here different, and whether the results from the previous grant supports the new approach
- Rationale for the use of organoids and why they are combined with RPE is unclear
- The nature of the organoids with regards to purity and quality of cells is unclear
- Description of rationale for choice of adhesives is minimal
- Complex approach
- More consideration of bioengineering aspects may improve consistency of product (e.g. eliminating the cutting of tissues with scissors)

DISCOVERY

Application #	DISC2-10745
Title (as written by the applicant)	Dynamic scaffolding system to enhance phenotype-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 functional cells for enhanced therapeutic applications.
Major Proposed Activities (as written by the applicant)	• Optimize stem cell culture scaffolds for enhanced functionality and biocompatibility. • Develop a high-throughput cell culture system with on-demand mechanically tunable scaffolds. • Determine the effects of dynamic cell culture on stem cell differentiation towards insulin-producing cells and their functionality.
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	$802,125
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 75

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

Mean	78
Median	75
Standard Deviation	8
Highest	95
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	3
(1-84): Not recommended for funding	12

Score Influences

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

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

- Addresses an important aspect of cell culture technology in an innovative way
- High impact
- Preliminary data are provided to support the aims and for both culture system design and manufacture and for culture and differentiation of iPSC into beta cells
- Addresses important scientific questions about the ECM biology and the proposed experiments should provide valuable information about forces that influence stem cell development
- A lot of solid preliminary data and the application is very well written
- Impressed with PI as a productive talented scientist who is asking important questions about the impact of ECM and biomaterials on biological processes
- Collaborators have impressive credentials and add to the strength of the project

Concerns

- These experiments are unlikely to make a make a major contribution to the diabetes goal of making better beta and other islet cells
- Concerns about need for the technology
- Mechanistic explanation of relevance could add clarity to application
- Details about how the technology will impact the field are missing - concerns about scalability
- Capacity for scale-up unclear
- Seems to be far from translation
- Preliminary data shows only a modest increase in marker expression
- No data on cell numbers, no data on whether maturation is enhanced or not

DISCOVERY

Application #	DISC2-10460
Title (as written by the applicant)	Mesenchymal stem cell extracellular vesicles as therapy for pulmonary fibrosis
Research Objective (as written by the applicant)	We propose to develop mesenchymal stem cell derived extracellular vesicles (MSC-EV) as treatment for lung fibrosis
Impact (as written by the applicant)	MSC-EV are promising for several lung diseases, but we need to better understand how they work, where they go in the body, and whether there is a subset of MSC-EV with better efficacy
Major Proposed Activities (as written by the applicant)	• To define the molecular characteristics, content, and effects of subsets of MSC-EV that do or don't express the Thy-1 protein • To define the distribution of Thy-1 positive and negative MSC-EV in the body in the setting of lung fibrosis, and define what cells they interact with • To compare the effectiveness of Thy-1(+) and Thy-1(-) MSC-EV in treating lung fibrosis of different causes, in comparison to existing treatments
Statement of Benefit to California (as written by the applicant)	There are estimated to be over 7000 individuals in California with idiopathic pulmonary fibrosis (IPF), an incurable and fatal disease. Current treatments only slow the disease progression, but do not cure IPF. Many of these individuals undergo lung transplantation which is very costly and at best adds a few years to life expectancy. Knowledge from this project may benefit other types of fibrosis such as liver fibrosis and heart failure.
Funds Requested	$2,013,760
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 75

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

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

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 the necessary significance and potential for impact?	7	4	2
Is the rationale sound?	3	6	4
Is the proposal well planned and designed?	0	7	6
Is the proposal feasible?	2	6	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

- Highly impactful line of investigation
- Thy-1 mediated mechanism is compelling
- System used is an exciting method to target cells
- Strong team

Concerns

- MSC controls and saline controls missing
- Determining proteomic differences between Thy1+ and Thy1- MSC-EV seem problematic; challenges not discussed
- Non-translational animal model
- Consideration of pitfalls and proposal of alternatives is limited for all three areas of investigation
- Fetal calf serum by centrifugation is not free of exosomes or xenobiotics
- Purification approach cannot be used to enter clinic

DISCOVERY

Application #	DISC2-10566
Title (as written by the applicant)	Off-the-shelf hypo-immunogenic iPSC-derived CAR-T-cells for allogeneic therapies
Research Objective (as written by the applicant)	To generate off-the-shelf iPSC-derived CAR-T-cells which effectively eliminate the tumor while avoiding an immune response (“hypo-CARs”) when transplanted into a genetically distinct individual.
Impact (as written by the applicant)	Patient-specific CAR-T cell generation is limited to special centers, and is time and cost intensive. Hypo-immunogenic CAR-Ts could be delivered to a genetically distinct (“allogeneic”) individual.
Major Proposed Activities (as written by the applicant)	• To generate human hypo-CAR-iPSCs and subsequent hypo-CAR-T cells. • To study the safety and efficacy of hypo-CAR-T cells to inhibit tumor growth in vivo. • To study the immune response to and survival of hypo-CAR-T cells in vivo.
Statement of Benefit to California (as written by the applicant)	Off-the-shelf CAR-T cells using hypo-immunogeneic iPS cells have potential to eliminate B cell malignancies and prevent immune rejection, eliminating costs and time of current CAR-T cell applications. Besides its enormous potential to improve the health of California residents, our breakthrough would also inevitably lead to licensing opportunities as well as FDA-approved cell therapy, which would generate significant future revenues for the State of California.
Funds Requested	$1,916,250
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 75

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

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

Score Influences

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

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

Is the proposal feasible?	0	8	7

Reviewer Comments

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

Strengths

- There is an unmet need for cheaper source of T-cells for CAR-T generation
- There is a need of technological advancement for generation of allogeneic CAR-T cells to reduce the timeline of treatment and this proposal is in line with addressing the key aspect of CAR-T based therapies
- Generation of iPSCs that can evade the immune response and rejection from an allogeneic host will greatly benefit patient care
- The successful generation of hypo-iPSC and the data on survival of mouse hypo-iPSC due to abolished NK cell killing is exciting
- CAR-T cells are exciting anti-cancer agents
- The proposed concept of manipulation to decrease immunogenicity is interesting
- The team is excellent and has T-cell expertise

Concerns

- Feasibility is a concern with no data on T-cell fate survival and longevity - need preliminary data for side-by-side comparison with currently used clinical protocols
- The maintenance of the T-cell fate generated from iPSC and their survival and functional longevity has not been extensively addressed and needs to be determined
- Hypo-iPSCs may not be equally competent to differentiate into T cells on OP9 or ATO culture systems; lack of knock-ins may have deleterious effects on T-cell differentiation
- There is a need for more preliminary data to address questionable feasibility and whether they are going to generate enough T-cells from the iPSCs
- It is not clear that adequate numbers of T-cells can be generated by the proposed system
- Although the proposal outlines the path of translation, more attention needs to be given to the timeline of production and obtaining cell numbers required for translation
- T-cells are likely to have different immunogenicity profiles compared to cardiomyocytes and iPS cells
- The need for off the shelf T-cells is not clear as current success rates generating autologous stem cells is high
- Previous studies have shown iPSC derived-CAR-T cells are effective for xenograft models as suggested by these investigators; whether these hypo-iPSCs are better than the autologous PBMC derived CAR-T needs to be established
- There has been a recent death and clinical trial hold for an allogeneic CAR-T cell product against CD123; how this product overcomes whatever the issues were in the current trial should be addressed

DISCOVERY

Application #	DISC2-10678
Title (as written by the applicant)	Adipose Derived Stem Cells Transduced With a Lentiviral Vector To Enhance Bone Repair
Research Objective (as written by the applicant)	Human adipose derived stem cells transduced with a lentiviral vector containing the cDNA for bone morphogenetic protein (BMP) and caspase 9 (inducible suicide gene).
Impact (as written by the applicant)	The treatment of severe fractures that occur with high energy trauma (i.e. car accidents and combat injuries) that are not often successfully treated with our present technology.
Major Proposed Activities (as written by the applicant)	• Compare efficacy of ASCs transduced via lentiviral gene therapy to express BMP-2 versus rhBMP-2 with respect to bone defect healing and quality of bone repair in an athymic rat model. • Identify if there is a change in the surface antigens of ASCs after transduction and determine if there is a subpopulation of cells with increased BMP production. • Determine if the BMP production by ASCs after lentiviral transduction is influenced by the age or gender of the patient cell source. • Assess systemic and local biodistribution of ASCs transduced with the lentiviral vector via quantification of vector copy number and vector integration analysis. • Pathological evaluation of internal organs for inflammatory response or cell necrosis to the viral vector and assessment for heterotopic ossification around the rat femur and systemically.
Statement of Benefit to California (as written by the applicant)	The ultimate goal of this project is to develop stem cell therapy with adipose derived stem cells to treat severe bone loss problems associated with high energy trauma (i.e. car accidents and combat injuries) that cannot be consistently resolved with our present technology. This clinical strategy will induce difficult fractures to heal to avoid amputation so patients can return to work and resume an active lifestyle.
Funds Requested	$2,124,849
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 75

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

Mean	74
Median	75
Standard Deviation	4
Highest	80
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

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

Reviewer Comments

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

Strengths

- The proposed idea is relatively straightforward
- Preliminary data suggests that the procedure will work
- Data indicates that more BMP can be produced from ASCs than bone marrow cells (~4X more protein produced)
- Strong preliminary data
- PI is very accomplished in the field

Concerns

- The main issue is that the plan is not much different than what has been done previously
- Unclear why over-expression of BMP-2 from ESCs will lead to enhanced bone repair, when BMP-2 has not worked that great to heal bones; a different delivery method will be used, but the underlying ability of BMP-2 to heal large bone defects is unclear
- The major innovation is the mode of delivery of BMP-2 to the damaged site; while this may solve the issues associated with previous approaches, it does not address the potential issue that BMP-2 is not the best choice to heal large bone defects
- The VEGF/angiogenic component for critical limb defects is not considered/discussed as comparator to the proposed product; other products using scaffolds and nanoparticle release of BMP-2 with tunable additional growth factors are also not discussed as comparator
- Poorly defined cell population
- Project 3 will analyze tissue to determine if the ASC treatment causes any issues.
    - A concern is the reported variability in rhBMP-2 expression in different patient cells (it looks like 5 different cell lines will be analyzed); an analysis of rhBMP-2 levels in these cells must be performed.
    - It appears that the 5 “groups” all use the same original transfected cells
- Ability to provide a standardized cell with normative cut offs is important to move forward to clinic
- Consistency of product does not appear to be prioritized: SVF and ASC differences may reflect relative enrichment of cells in ASC; a standardization by CFU as proposed by ASTM guidelines and adopted by the FDA is not discussed
- Caspase 9 system may not be required: there is no data to suggest that transfected cells once differentiated into bone continue to produce BMP-2 and no data to suggest that adipose cells persist and continue to produce systemic BMP-2- some data presented show cells reduce over time so not clear why the concern is there - justification is missing
- Need larger animal model to test vascularity issues when dealing with large bone defects

DISCOVERY

Application #	DISC2-10773
Title (as written by the applicant)	A screen for drugs to protect against chemotherapy-induced hearing loss, using sensory hair cells derived by direct lineage reprogramming from hiPSCs.
Research Objective (as written by the applicant)	Development of a screen using inner ear sensory hair cell-like cells made by direct lineage reprogramming, for discovering drugs to ameliorate hearing loss during cancer chemotherapy.
Impact (as written by the applicant)	Hearing loss, both adult and pediatric, due to life-saving cisplatin chemotherapies. Also, Cockayne syndrome which includes a hearing loss component and hypersensitivity to cisplatin.
Major Proposed Activities (as written by the applicant)	• Develop and optimize induced human hair cell-like cell screening technology for cisplatin ototoxicity (Aim 1), for use in otoprotectant screening (Aim 2) and disease modeling (Aim 3). • Test previously identified otoprotectants (Vlastis et al., 2012) in human iHC screen with requisite otoprotective effects ("hits") against an LD50 dose of cisplatin (Aim 2). • Screen a 2500-compound library of FDA-approved drugs (Enzo Life Sciences) in human iHC screen for requisite otoprotective effects ("hits") against an LD50 dose of cisplatin. • Develop hair cell reporter lines from Cockayne Syndrome patient cells, and characterize human iHC disease models of cisplatin hypersensitivity in Cockayne Syndrome hair cells. • Test whether otoprotectants identified in Aim 2 confer protection against cisplatin ototoxicity in human iHC disease models of ototoxicity hypersensitivity
Statement of Benefit to California (as written by the applicant)	Cancer in both children and adults is frequently treated with chemotherapy agents that have a high potential to damage hearing. When this occurs in children, significant developmental delays require expensive rehabilitation and special education. Since regeneration does not occur, adults are frequently left with permanent hearing loss. This proposal uses state-of-the-art stem cell techniques to develop a screen to discover drugs that prevent hearing loss due to life-saving chemotherapy.
Funds Requested	$1,167,600
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 75

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

Mean	74
Median	75
Standard Deviation	2
Highest	75
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

Score Influences

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

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have the necessary significance and potential for impact?	10	2	2
Is the rationale sound?	4	7	3
Is the proposal well planned and designed?	1	9	4
Is the proposal feasible?	3	6	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

- Hearing loss after cisplatin chemotherapy is a serious morbidity in cancer patients who were given effective but toxic cisplatin to treat their cancer; this proposal may identify new compounds or FDA-approved drugs that have the ability to protect hair cells in the inner ear from cisplatin ototoxicity
- The studies proposed in this application could lead to translation of newly identified compounds as effective adjuvant treatment to mitigate hearing loss associated with cisplatin chemotherapy
- Interesting approach, important problem
- Impact is high
- Exciting preliminary data demonstrating induced reprogramming of iHC in mouse and human

Concerns

- Human iHC have been less characterized; key data whether human iHC are sensitive to cisplatin or how different from mouse iHC is not shown
- Important preliminary data on human cells to support feasibility is needed
- Preliminary data in humans is underdeveloped
- A seemingly low efficiency of generating human iHC (Figure 5C) is a concern; assuming cell viability will be measured by capturing GFP, it is not clear what is the sensitivity and limitation of detection; this can be a bottleneck of the assay if iHC cell number is low from the beginning
- It is unclear whether their cells are predictive of outcomes on iHCs in vivo

- Adequate controls for the screen are needed
- The screen needs to include cancer cells as there is no value to protective agents that also protect cancer cells; evidence that they can find cells that provide selective protection would be helpful
- Preliminary data does not show that the sensitivities are specific for these cells - comparative data with non-toxic, but similar agents would be useful
- The applicants should obtain some preliminary animal data which will allow them to advance to selecting a candidate for translation

- It is unclear how cisplatin will be combined with other agents
- It is not clearly described how exactly the applicants will approach ensuring anti-cancer activity of cisplatin when protective agent is combined; this is a concern particularly because the applicants mentioned that cisplatin-DNA adducts may mediate toxicity to HC, which appears analogous to toxicity to cancer cells
- Patients are treated with cisplatin for months, and thus any drug has to be suitable for long-term administration
- The drug also needs to get into the ear unless they figure out a way to do local release that would be useful over the period of months
- The applicant would benefit greatly by working with people skilled in pharm/tox and drug development; there is much more to a project like this than the initial screening assay
- A cancer pharmacologist would be a helpful addition to the team
- Team should have expertise in pharm/tox and drug screening

DISCOVERY

Application #	DISC2-10609
Title (as written by the applicant)	Development of dual gate chimeric antigen receptor T cell therapy for lethal neuroendocrine prostate cancer
Research Objective (as written by the applicant)	We will develop combinatorial chimeric antigen receptors (CAR) targeting CEACAM5 and Trop2 to generate a safe dual gate CAR-T cell therapy to treat aggressive neuroendocrine prostate cancer.
Impact (as written by the applicant)	If successful, a dual gate CEACAM5/Trop2 CAR-T would benefit patients with neuroendocrine prostate cancer as a safe and targeted therapy for a deadly disease without standard therapies.
Major Proposed Activities (as written by the applicant)	• Functional identification of Trop2 inhibitory CARs that blunt T cell activation by screening a Jurkat NFAT reporter cell line. • Functional prioritization of dual gate CEACAM5 activating and Trop2 inhibitory CAR combinations in a Jurkat NFAT reporter cell line. • Evaluation of the antigen-dependent cytotoxicity of CEACAM5/Trop2 CAR-T cells upon co-culture with neuroendocrine prostate cancer and normal human cell lines. • Determine the anti-tumor activity of dual gate CEACAM5/Trop2 CAR-T cells on neuroendocrine prostate cancer xenograft tumors in immune-deficient mice. • Develop a transgenic/knock-in mouse model (CEABAC2/hTrop2-KI) with human CEACAM5 and Trop2 expressed in a physiologic manner. • Determine the safety and efficacy of CEACAM5/Trop2 CAR-T in immune-competent mice that express human CEACAM5 and Trop2.
Statement of Benefit to California (as written by the applicant)	The proposed research will benefit the State of California and its citizens by advancing the development of a new immune therapy for deadly neuroendocrine prostate cancer based on a novel strategy that focuses on selectivity and safety. We will use targeted chimeric antigen receptor T cell (CAR-T) technology but introduce a dual gate logic system to enhance the regulation of immune cell activation and specific killing of tumor cells.
Funds Requested	$1,540,221
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 75

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

Mean	73
Median	75
Standard Deviation	3
Highest	75
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

Score Influences

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

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have the necessary significance and potential for impact?	5	5	3
Is the rationale sound?	0	7	6
Is the proposal well planned and designed?	2	6	5
Is the proposal feasible?	0	4	9

Reviewer Comments

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

Strengths

- The proposed work is based on very exciting published work showing the extremely powerful potential of CAR-T cells as an effective anti-tumor therapeutic
- Although most of the evidence and scientific rationale for CAR-T use has been in leukemia and lymphoma treatments, there is recent success with targeting solid tumors, making the proposed work an important avenue of research
- The use of CAR-T in solid tumors would be exciting
- The dual CAR-T cell concept is intriguing
- The CEACAM5 is a new antigen candidate
- The team is excellent
- The research is outstanding, with the PI being a leading figure in cancer/stem cell biology

Concerns

- The expression of the target antigen is variable; this suggests that CEACAM5-negative tumor cells likely exist even in patients with CEACAM5 positive disease that would be a means of therapeutic escape
- The CEACAM5 antigen needs to be better characterized; the complexity of the non-specificity of CEACAM5 as a tumor antigen (found on a lot of tumor cells) is very difficult; this antigen is certainly not as good a candidate as CD19 as in B cell neoplasms

- The proposed work is not directly related to the use of human stem/progenitor cells or iPSCs, rather it deals with the use of mature T cells, which can show stem like function when induced into a memory state; however, the proposal does not directly address how T stem cell memory will be induced or purposed in their experimental approach, or directly test whether a Tscm carrying CARs would show a different functional capacity as part of Aims 2-3
- The argument regarding Tscm is weak; there are no studies proposed that actually study these cells

- The proposed work is structured into 3 aims, with the first aim screening for the functionality of different CARs using a Jurkat T cell line; although this can be a convenient approach, it is not clear whether this would be the best way to test either inhibitory or stimulatory responses, or how the combination would translate to normal T cells
- Relating to the use of Jurkat T cells, there is a missed opportunity to use that approach in combination of dose response of anti-CD3 stimulation when testing the effectiveness of Trop2 iCAR.
- The use of Jurkat cells is questionable as mature peripheral blood T cells are readily available
- The proposed work and milestones are feasible, but the need for Aim 1 is not very well supported, and as pointed out by the authors, testing the CARs directly on PBMC T cells would make the most sense, as Jurkat T cells may not offer a true reflection of how a normal T cell may respond

DISCOVERY

Application #	DISC2-10507
Title (as written by the applicant)	A comprehensive strategy to non-invasively monitor the pharmacokinetics of stem cell-derived therapies in patients
Research Objective (as written by the applicant)	We propose to develop new methods and tools for visualizing stem cells or stem cell-based therapies in patients
Impact (as written by the applicant)	Knowing where cells go upon injection into patients will be critical for their successful use to treat disease. Current methods for monitoring cells in patients are not fully optimized or validated.
Major Proposed Activities (as written by the applicant)	• Optimize the accumulation of PET tracers in 9 different stem cells or stem cell-derived primary cells • Determine the lower limit of detection for imaging the cell type – tracer combination in vivo • Quantify the degree of correlation in vivo between absolute cell numbers and quantified PET values
Statement of Benefit to California (as written by the applicant)	Stem cell-based cellular therapies have the potential to treat important diseases suffered by Californians. However these therapies are also complex and will require specialized tools to monitor their behavior in patients. The proposed research focuses on developing, optimizing, and validating methods for visualizing stem cell-based cellular therapies after they have been injected into patients. We anticipate that this tool will enable the better use and faster deployment of these therapies.
Funds Requested	$1,072,581
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 75

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

Mean	71
Median	75
Standard Deviation	7
Highest	80
Lowest	60
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

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 the necessary significance and potential for impact?	8	3	3
Is the rationale sound?	4	4	6
Is the proposal well planned and designed?	4	8	2
Is the proposal feasible?	3	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

- Tracking cells is clinically important
- Significance: we need to know where stem cells go after transplantation (in vivo stem cell tracking)
- The strength of the proposal is the significance of the problem and the expertise of the investigator
- A tool to assist in understanding proliferation, differentiation, and migration would be very helpful
- Proposed approach to finding tracers is well described

Concerns

- Cell types are not well-justified; should focus on currently used cell types used in cell therapy
- A specific rationale for choosing the proposed cell types is lacking; specific cell lines need to be identified together with a rationale for each
- The limit for the detection is approximately 70 hours from the list of radioisotopes presented, so while this technique will identify the location of the injected cells, it will not track them for a long enough duration to determine their fate
- Duration of labeling/half-life and duration of in vivo tracking is a concern
- Cell number correlation to radioactivity is not well-defined
- Differentiation between dead and live cells is not discussed

DISCOVERY

Application #	DISC2-10456
Title (as written by the applicant)	Manipulation of the skeletal stem cell niche for articular cartilage regeneration
Research Objective (as written by the applicant)	To devise a new method for articular cartilage repair, through better understanding of the effects of surgical, chemical and cellular control of Skeletal Stem Cell (SSC) activity.
Impact (as written by the applicant)	By manipulation of the SSC niche within a cartilage defect, we aim to reverse the effects of OA and regenerate healthy articular cartilage to restore joint function.
Major Proposed Activities (as written by the applicant)	• Using surgical manipulation with Microfracture (MF) to stimulate expansion and activation of skeletal stem cells (SSC) for cartilage repair. • Use FDA approved compounds including Infuse (BMP2) and Avastin (VEGF inhibitor) to direct MF- activated SSC towards articular cartilage regeneration to reverse the effects of Osteoarthritis (OA). • Develop methods for autologous adipose stromal cell stimulation and transplantation a source of induced SSC (iSSC) to augment MF-activated SSC for cartilage repair.
Statement of Benefit to California (as written by the applicant)	By 2040, 78.4M Americans (9.5 M Californians) will be diagnosed with arthritis. OA is the most common arthritis that often affects the joints of the hands, hip and knee. Using a combination of FDA approved techniques and innovative regenerative surgery approaches; our disruptive SSC-based therapy can reverse cartilage damage in OA. This ultimately will improve patient's quality of life while reducing the estimated cost burden of OA in the USA , including 60 Billion USD annually to California.
Funds Requested	$2,145,611
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 70

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

Mean	71
Median	70
Standard Deviation	3
Highest	75
Lowest	65
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have the necessary significance and potential for impact?	7	1	5
Is the rationale sound?	4	3	6
Is the proposal well planned and designed?	1	7	5
Is the proposal feasible?	0	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

- Cartilage damage is a clearly unmet medical need, as ALL therapeutic alternatives at disposal generate suboptimal long-term clinical results, both phenotypically and functionally
- Addresses a clinical unmet medical need
- High unmet need
- The identification of an adult chondroprogenitor capable of producing a permanent type of cartilage with closer resemblance to articular cartilage (after manipulations), and not transient cartilage, is of huge relevance
- Inducing articular cartilage would be very useful
- Novel approach to OA
- Great background data in mouse
- The quality of the study is unquestionable; the proposed experiments involve state-of-the-art techniques and the information that results from them is of high value
- Outstanding investigator with great seminal works

Concerns

- While very innovative, not clear on specifics on how it may be translated to clinic
- Even though SSC might not be MSC per se, a potential overlap between SSC and MSC subpopulations that have been identified, sharing similar markers (e.g., CD146), was overlooked
- They contrast SSC and MSC used in previous cell therapies for OA arguing that none of these cells are stem cells:
    - Culture-expanded MSC used in such studies involving cartilage general damage (e.g., OA) are not expected to work as chondroprogenitors, but rather to exploit their immunomodulatory and trophic activities to alter the joint microenvironment
    - The comparison would be valid if using MSC to engineer a cartilage implant to treat a focal chondral or an osteochondral defect
- The data in mice is strong and convincing; the human preliminary data is still under revision, and only one figure was included in the application, which leaves a significant portion of the supporting information pending validation
- Paper in revision does not provide adequate specifics
- The reliance on unpublished data in animal and human models not necessarily relevant to OA is a concern
- Clarity on design is needed
- It is not clear why numerous in vitro aims are proposed in Aim 1 as the preliminary data that the PI has presented was used to argue that the treatment will work in vivo
- In Aim 2, the team does not appear to have a plan to deliver BMP2 and VEGFi to the MF site
- The biomaterial proposed to be used is still under development, which may have an impact on the final cell-based product.
- Scaffold not described - biomaterials are still under evaluation
- Biomaterials are not specified
- The team is “currently evaluating” a number of biomaterials

DISCOVERY

Application #	DISC2-10749
Title (as written by the applicant)	iPSC derived neural progenitor cell therapy for juvenile macular dystrophy
Research Objective (as written by the applicant)	Grafted iNPCs preserve existing vision without cell replacement, reduce accumulation of lipofuscin in RPE by taking in outer segments, so disease progression is slowed down or even halted in STGD.
Impact (as written by the applicant)	Grafting iNPCs to preserve existing vision without RPE replacement in Stargardt disease (STGD) will slow down/halt disease progression and preserve vision, this will have huge impact to the field.
Major Proposed Activities (as written by the applicant)	• 1) Cell production: Culture iNPC, RPE and have enough cells for experiments. 2) Head to head comparison on the efficacy of subretinal injection of iNPC and RPE into mouse model for STGD • 1) To investigate whether vision rescue by iNPCs will be long term compared with RPE cells 2) To determine whether injection of iNPCs and RPE cells at the late stage of disease is still effective • 1) To determine the gene expression changes of grafted iNPC at early and later time points after transplantation 2) To set up meeting with FDA, prepare grant application for an IND enabling study
Statement of Benefit to California (as written by the applicant)	Children diagnosed with STGD are most in need of vision preserving therapies. Visual deficits affect patients' mental health and quality of life. Finding effective, safe mutation-independent treatment for STGD will help patients and reduce the economic burden . A suggestion of benefit from phase I trial on STGD subjects would greatly increase the medical significance of expanding the treatment to other macular dystrophies, this will attract for profit support, increase employment in California.
Funds Requested	$1,832,527
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 70

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

Mean	66
Median	70
Standard Deviation	7
Highest	75
Lowest	50
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

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 the necessary significance and potential for impact?	4	7	3
Is the rationale sound?	0	10	4
Is the proposal well planned and designed?	0	8	6
Is the proposal feasible?	2	5	7

Reviewer Comments

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

Strengths

- Good preliminary data in rat model

Concerns

- Promising results may be dependent on the specific preclinical model - concerns about relevancy and translatability to humans
- Mode of action is not understood very well - preliminary data might be animal specific or phenotype specific which may influence outcomes
- Control cells may not be a good control for RPE cells because iPSC/ESC work much better
- Comparison with established RPE line not ideal
- Safety of graft not considered
- Work on safety/toxicity should be considered
- Pitfalls not well discussed

DISCOVERY

Application #	DISC2-10478
Title (as written by the applicant)	Exosomes from cardiac progenitor cells targeted to treat heart failure
Research Objective (as written by the applicant)	We propose studies to explore modified cardiac stem cell-derived exosomes as a next-generation therapeutic candidate for delivery to sites of cardiac injury to treat heart failure.
Impact (as written by the applicant)	Heart Failure is a disease affecting ~5M Americans. We propose to engineer highly potent cardiosphere-derived cell's exosomes to treat this disease by enabling the growth of new healthy heart tissue.
Major Proposed Activities (as written by the applicant)	• Generate Cre-loaded CDC exosomes and validate their function in vitro using mTmG mouse tissue explants treated with Cre-loaded CDC exosomes and fluorescence conversion monitored. • Deliver Cre-CDC exosomes systemically by IV injection to mTmG mice and assess biodistribution by monitoring the tissue sites and rates of cellular red-to-green reporter conversion. • Generate CDC cell lines with engineered lentiviral constructs to produce exosomes with targeting surface display proteins and Cre-mRNA cargo to target injured myocardium. • Cloaking CDC exosome surfaces with targeting peptides and antibodies to enhance trafficking to ischemic tissues. • Evaluate the targeting efficiency of engineered Cre-CDC exosomes in vitro using mTmG fibroblasts or neonatal rat ventricular myocytes under oxidative stress to model ischemia. • Assess Cre-CDC exosome biodistribution and therapeutic effect in animal models of ischemic injury using IV doses of engineered or unmodified control Cre-CDC exosomes following AMI.
Statement of Benefit to California (as written by the applicant)	In 2016, the burden of Cardiovascular Disease (CVD) in California accounted for one in three deaths in the state. One in three adults (~8 million) Californians have some form of CVD, with the annual health care costs for CVD in California reaching an estimated at $37 billion. The human heart has limited capability to heal itself after tissue injury. We plan to develop cardiosphere-derived exosomes as a next-generation therapeutic to treat injured hearts and enable the growth of new myocardium.
Funds Requested	$1,677,130
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 65

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

Mean	66
Median	65
Standard Deviation	7
Highest	80
Lowest	60
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

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 the necessary significance and potential for impact?	7	6	0
Is the rationale sound?	3	9	1
Is the proposal well planned and designed?	1	9	3
Is the proposal feasible?	1	7	5

Reviewer Comments

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

Strengths

- Understanding the specific distribution of exosomes is a strength of this application
- Addresses some major questions in the field
- Well-developed technologies
- The use of mTmG model, although not translational, is likely to yield specific information on the cell types affected

Concerns

- The path to quickly translate into human clinical applications is unclear
- Mechanisms are not clear
- Lack of control of viral release from exosomes is a concern
- Lack of data or proposed studies aiming to characterize the effect of loading exosomes with viral particles on the exosome cargo and function is a concern
- Endpoints are likely to have high variability due to heterogeneity of exosomes
- Heterogeneity with vesicles is problematic
- Overly ambitious

DISCOVERY

Application #	DISC2-10487
Title (as written by the applicant)	Assessment of Novel Depots of Adipose-Derived Stem Cells for Chronic Rotator Cuff Injury
Research Objective (as written by the applicant)	To show that fat-derived stem cells collected from around our muscles is a safe cell source for repairing chronic rotator cuff injuries that is better at regeneration than other common fat sources.
Impact (as written by the applicant)	Develop an adult stem cell-based intervention to be used in concert with surgical repair that will encourage muscle regeneration and prevent re-tearing of the rotator cuff.
Major Proposed Activities (as written by the applicant)	• Evaluate the equivalency of fat tissue and fat-derived stem cells from regions that surround the upper trunk muscles and from the abdomen in humans and rabbits. • Establish the degree of improved regenerative potential of stem cells derived from fat surround the rotator cuff muscles compared to abdominal fat. • Establish why fat from around our muscles is better at regeneration by assessing immune response, tracking stem cell location, and correlating position and amounts with tests of muscle function. • Consult with internal and external teams of scientists on project outcomes and conduct preliminary meeting with FDA to discuss establishing a clinical trial.
Statement of Benefit to California (as written by the applicant)	More than a half million Californians live with chronic rotator cuff tears. While there have been improvements in surgical repair methods, re-tear rates are as high as 50% in the decade following surgery. Degeneration of cuff muscles limit the success of surgical repair, so here we will use metabolically active fat from around rotator cuff muscles to develop an injectable cell population that regenerates muscle in conjunction with surgical repair, thus increasing patient quality of life.
Funds Requested	$1,870,533
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 65

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

Mean	66
Median	65
Standard Deviation	4
Highest	70
Lowest	60
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have the necessary significance and potential for impact?	7	6	2
Is the rationale sound?	4	7	4
Is the proposal well planned and designed?	0	10	5
Is the proposal feasible?	0	9	6

Reviewer Comments

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

Strengths

- The harvesting of cells executed during the same surgical procedure as the rotator cuff repair provides a significant advantage to patients by reducing the exposure to multiple procedures and additional donor site morbidities
- The strength of the proposal lies in the applicability of the adipose cells harvested at the time of surgery; this is an attractive and feasible option for this disorder
- High impact due to high prevalence
- If successful, these cells could provide an attractive treatment approach
- Feasible for clinical application
- Clinical applicability

Concerns

- Despite the fact that the authors mention that in their experience rabbit-derived Adipose-Derived Stem Cells (ADSC) are functionally equivalent to their human counterpart, this does not necessarily align with other groups findings
- Experimental evidence that the proposed cells are better than previously used cells is needed; simply using a new or different cell line is not sufficient
- At this time, preliminary data not complete enough to warrant exploration
- Data regarding engraftment is needed to support the premise
- Preliminary data to support feasibility of milestone 3 is needed
- The differentiation potential of these cells is still questionable
- It is not clear that the proposed cells have the capacity to differentiate; the cells need to be more comprehensively characterized
- The main concern is that the differentiation potential of these cells is highly questionable.
    - While the phenotype of improvement in outcome may be valid, it’s highly unlikely that these cells differentiate to muscle cells
    - In the absence of fate mapping studies, this argument is not valid
    - The applicant should focus on perhaps other paracrine-like mechanisms which may mediate induction of endogenous repair mechanisms

DISCOVERY

Application #	DISC2-10605
Title (as written by the applicant)	Stem Cell-based Modeling and Therapeutic Targeting of IDH Mutant Gliomas
Research Objective (as written by the applicant)	Using stem cell and progenitor-based models to repurpose therapeutics that show specificity against IDH1 mutant glioma cells while sparing regenerative cell populations in the adult brain.
Impact (as written by the applicant)	The proposal will generate lacking pre-clinical tools to study IDH1 mutant gliomas and repurpose pharmaceuticals as an accelerated approach to improve the outcome of glioma patients.
Major Proposed Activities (as written by the applicant)	• High-throughput screening of approved and "known bioactive" compounds to link therapeutic response to IDH1 mutation status in human gliomas and neural stem/progenitor cells. • Engineer human induced pluripotent stem cell-derived neural stem and progenitor cultures as glioma models of genetic simplicity with genetic alterations defining IDH1 mutant glioma subgroups. • Use human gliomas and iPSC models to evaluate whether compounds from high-throughput screen show specificity in reducing viability of 1p:19q:TERT versus ATRX:TP53 gliomas displaying IDH1 mutation.
Statement of Benefit to California (as written by the applicant)	Glioma is the most common primary malignant brain tumor, with approximately 1/3 of all gliomas displaying IDH1 mutation. This pioneering work will use human induced pluripotent stem cells and patient-derived tumor cells to establish pre-clinical models of IDH mutant gliomas that are currently lacking. High-throughput screens of approved and bioactive compounds represent an accelerated approach to improve outcome in glioma patients and reduce the cost for the State of California.
Funds Requested	$2,212,924
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 65

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

Mean	64
Median	65
Standard Deviation	4
Highest	75
Lowest	60
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have the necessary significance and potential for impact?	6	4	3

Is the rationale sound?	1	9	3
Is the proposal well planned and designed?	2	7	4
Is the proposal feasible?	1	7	5

Reviewer Comments

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

Strengths

- Glioblastomas have few effective therapies
- IDH mutant glioma is a lethal brain malignancy and lack of effective treatment is an unmet medical need; this proposal could identify candidate compounds that have selective activity for these gliomas and may enter clinical trials based on the outcomes of this proposal
- Repurpose of existing drugs for treatment is a strength
- Models are established

Concerns

- The applicants have identified a potentially interesting selective compound, but it is not described how the research team will approach this for validation and further development
- Not clear what the cell model and the preclinical models for testing will be and whether they are good models for testing drug candidates
- The applicants propose an extensive use of animal models; how to select/prioritize or not select models to be used is not systematically described
- It is not clear that the models generated will recapitulate human disease; that recapitulation should occur prior to use as a screening tool
- Validation for relevancy to human tumors is limited
- Considering the ease with which gliomas grow in vitro, and the multiple thousands of human lines available around the world, the lack of suitable IDH mutant lines suggest that this is not a particularly important mutation in tumor maintenance
- It is not clear how the hits, if any, will be prioritized for testing in animal models, and how many compounds and how many models will be used
- Some critiques from prior review not addressed- i.e. prioritization of hits and justification of priority not identified

- It is not clear based on what they show whether the applicants have sufficient experience in the generation of gene mutations and animal studies with orthotopic models
- There are far too many places for the proposal to fail, including the need to find drugs, for the drugs to cross the BBB, for tumors to retain dependence on IDH mutation, and for the artificial tumor model they use to be relevant to human tumor biology
- This proposal involves steps: model creation, identification of hits via in vitro HTS, validation and selection of hits, and testing in animal models, which is expected to be time consuming; the completion of this proposal will take time, most likely more than 2 years; the focus on already identified compounds may potentially accelerate translation, but the applicants did not elaborate this matter
- Extremely ambitious program for 2 years

DISCOVERY

Application #	DISC2-10623
Title (as written by the applicant)	Discovery of novel and personalized treatments for Parkinson's disease using IPSC-derived dopaminergic neurons
Research Objective (as written by the applicant)	Identification of a series of 3-5 therapeutic candidates for the treatment of Parkinson's disease (PD) using phenotypic screening in engineered and patient-derived iPSc-converted DA neurons
Impact (as written by the applicant)	Complex diseases such as PD are difficult to model and have not been addressed by target-directed discovery approaches. Our approach in patient-derived cells provides an unbiased path to treatment.
Major Proposed Activities (as written by the applicant)	• Identify screening hits and their targets using an engineered human IPSC-derived dopaminergic neuron system • Test hits in a series of Parkinson's disease patient-derived cells to verify effectiveness and confirm target identification • Optimize the potency and selectivity of these hits for the disease • Convert the hits into drug-like lead compounds for animal testing • Test lead compounds in PD animal models
Statement of Benefit to California (as written by the applicant)	PD is a complex disease affecting 1-3 in 1,000 and increasing by 50% in 2030. The disease complexity makes it difficult to model and is no doubt responsible for the paucity of therapeutic options available. Our approach using IPSC-derived human dopaminergic neurons tests for phenotypic changes directly in diseased cells which eliminates this variable. Identification of new therapies will improve the lives of Californians and all PD patients. It is also potentially applicable other CNS diseases.
Funds Requested	$1,399,076
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 65

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

Mean	64
Median	65
Standard Deviation	12
Highest	90
Lowest	40
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	1
(1-84): Not recommended for funding	14

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have the necessary significance and potential for impact?	10	3	0
Is the rationale sound?	3	8	2
Is the proposal well planned and designed?	1	11	1

Is the proposal feasible?	1	7	5

Reviewer Comments

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

Strengths

- The chemistry is clearly very good
- Interesting technology
- Great strategy because
    - This is a creative way to come up with brand new out-of-the-blue structures that resemble nothing like what has come before, and potentially open up new vistas of pharmacological diversity
    - Methodology potentially samples a much larger region of structure space
    - Cheaper
- May lead to novel compounds because of solid chemistry
- Great team

Concerns

- The drug discovery efforts are far too restricted to a limited number of cell lines, particularly as a fine reading raises the concern that they are working with SCNA lines of which three are from the same patient
- If the hypothesis is to find a molecule that generally protects dopaminergic neurons against 'nonspecific' stress, a screen against a wide variety of stressors (environmental, multiple genetic) is needed; as presented, the proposal will test against a single genetic stress
- The core hypothesis for the mechanism of action of whatever emerges from the screen is unclear; design the screen around the best way to test a well-defined hypothesis
- Screening for mechanism to identify new compounds appears to be limited in scope- compounds may be restricted in application
- The animal models suggested are the wrong ones for analyzing drugs that might work on SCNA mutants
- The stressor used in vitro is of questionable relevance to PD, and the biological outcomes studied are very limited
- Lacks serious biological assessment of compounds thus translational component is missing
- Milestone 5 is unclear; it should be removed or explained in more detail, with clear demonstration of expertise, resources, statistics, and experimental design to be successful
- Terms need to be well defined and explained; for example, it is not really clear what the tool is, and it is really hard to find more explanation on the web or in the literature
- Marketing jargon in grant detracts from defined scientific design; consider avoiding use of terms that require the trademark symbol
- Very small percent effort; it is hard to believe key personnel would have the time to oversee the project at 1% effort
- Many reviewers will be from academic backgrounds; having some academics not involved in the proposal read revisions is recommended

DISCOVERY

Application #	DISC2-10733
Title (as written by the applicant)	Engineered mesenchymal stem cells for combinatorial cancer immunotherapies
Research Objective (as written by the applicant)	We are developing genetically modified stem cells to treat ovarian cancer.
Impact (as written by the applicant)	This work focuses on ovarian cancer, and if successful, the technology can be applied to other solid tumors (e.g. pancreatic, glioma, lung) in the future.
Major Proposed Activities (as written by the applicant)	• Genetic engineering of stem cells to express various therapeutic molecules • Cell based (in vitro) screening for anti-cancer effect of candidates • Characterize function of anti-tumor stem cells in pre-clinical models of ovarian cancer
Statement of Benefit to California (as written by the applicant)	There is a tremendous unmet need for new and effective therapies for ovarian cancer. In the State of California, it is estimated that there are over 2,000 new cases of ovarian cancer per year with over 1,300 deaths and an annual economic burden of $60M (based on 2013 CDC data). Successful development of a stem cell based therapy for cancer will also support job growth in R&D, manufacturing, and biopharma supporting the novel treatment modality.
Funds Requested	$1,831,126
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 65

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

Mean	64
Median	65
Standard Deviation	11
Highest	75
Lowest	30
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

Score Influences

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

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

Reviewer Comments

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

Strengths

- Problem is very impactful
- Augmentation of cancer therapy for ovarian cancer
- The idea of immune stimulation locally with a cell delivery method is interesting
- The delivery of immune modulators to solid tumors is challenging and the proposed use of MSCs as delivering agents might work if effective concentrations of the therapeutic agents in the tumor microenvironment of the is achieved
- Incredible data with genetically modified MSCs
- Team is accomplished

Concerns

- The proposed use of immunomodulatory MSC in this proposal offers promise, however the lack of detailed mechanism-based studies on a few novel combinations dampens the enthusiasm of this application
- The studies are not hypothesis driven
- Not clear that MSCs are a good delivery model
- Homing to tumor not assured
- No data to show that the produced cell is not susceptible to the released factor
- It is unclear how long the cells survive and whether the producer cell is susceptible to the drug being released
- Given the complexity of the immune profile of tumors, simultaneous delivery of all MSC payloads might not be the best strategy
- The composition of the recruited immune cells and their activation status varies between tumors of the same; the use of one syngeneic model might not cover the tumor heterogeneity seen in patients
- Different tumors will have different tumor microenvironments
- Rationale for combinations selected may not be applicable between breast and ovarian tumors
- The combinations of payload have little rationale
- Mechanism for each selected payload is limited
- Chemokines suggested by the investigators for attracting T cells also attract suppressor cells
- The syngeneic tumor model proposed in the study has not been established by the investigators; insufficient preliminary data relevant to the proposal has been demonstrated
- Data from the clinical trial will be useful
- The design of the project does not allow the selection of a lead candidate ready to advance to translation
- No rationale for table 1 (taken from nature review)

DISCOVERY

Application #	DISC2-10596
Title (as written by the applicant)	Development of Vasculature from iPSCs
Research Objective (as written by the applicant)	The endothelial and smooth muscle lineage cells will be derived from human induced pluripotent stem cells to reconstitute vasculature and restore blood perfusion in ischemic tissues.
Impact (as written by the applicant)	Critical limb ischemia represents a significant unmet medical need without effective medical therapies for patients at high risk of amputation, and it may be alleviated by hiPSC-based cell therapy.
Major Proposed Activities (as written by the applicant)	• Derive endothelial lineage cells from human iPSCs and determine the optimal type for vessel formation in a xenograft mouse model of hind limb ischemia. • Investigate whether the combination of hiPSC-derived endothelial cells and vascular smooth muscle progenitor cells further enhances restoration of the vascular network in ischemic mouse limbs. • Enhance engraftment of the hiPSC-derived vascular cells in hind limb ischemia xenograft mouse model using a specific survival factor cocktail or hypoxia preconditioning to achieve therapeutic effects. • Evaluate the therapeutic effects of the hiPSC-derived vascular lineage cells on restoring blood perfusion in an HLI model of aged mice.
Statement of Benefit to California (as written by the applicant)	Critical limb ischemia (CLI) is a severe peripheral vascular disease with high risk of amputation, high morbidity and mortality. Approximately 120,000 low extremity amputation procedures are performed annually in the US. The annual cost for these patients is estimated at $4 billion. Therefore, there is a significant unmet medical need to develop new therapies for CLI. We propose to develop a novel human iPSC-based cell therapy to treat CLI, from which patients in California will benefit.
Funds Requested	$1,855,539
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: --

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

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

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 the necessary significance and potential for impact?	5	7	1
Is the rationale sound?	1	11	1
Is the proposal well planned and designed?	0	11	2
Is the proposal feasible?	0	9	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

- Creating a vasculature is a novel undertaking
- If procedure works, it would generate cells that could be used to create blood vessels

Concerns

- Serious technical concerns as the many iterations proposed here represents an amalgam of therapeutics where we will not be able to probe the source of the functional benefits
- Unclear why Milestone 1, where pure populations of endothelial lineage cells at different stages will be injected into the mouse model, is proposed:
    - In intro, PI says this doesn't work
    - In Aim 2 the combined hiPSC-VSMPs and hiPSC-ECs approach will be used
- Vascular smooth muscle progenitor (VSMP) cell role not clear and will not be dissected
- Milestone 3 uses hypoxia to pre-treat cells; no preliminary data to show that this will have any effect
- Survival factors not well-justified
- Milestone 4 will repeat the experiments in aged mice; this is ambitious under the two-year funding model (partially acknowledged by the PI)
- Older mouse model not justified; not clear that there are phenotypic differences
- PI proposes too many experiments; it is not clear which are the important experiments
- Proposal is not supported by preliminary data
- Not responsive to prior critiques
- Senior person is co-investigator

Recommendations

- Proposal could be streamlined; for example, removal of Aims 1 and 4
- Removal/refinement (i.e. justification) for hypoxia experiments

DISCOVERY

Application #	DISC2-10715
Title (as written by the applicant)	Spinal multisegmental stem cell delivery for treatment of amyotrophic lateral sclerosis.
Research Objective (as written by the applicant)	The therapeutic candidate is a stable human fetal cortex-derived cell line. This stem cell line line was derived with informed consent in a manner compliant with guidelines of the NIH and the FDA.
Impact (as written by the applicant)	The use of therapeutic candidate and novel subpial cell delivery technique may accelerate the cell-replacement-based treatment of amyotrophic lateral sclerosis and spinal traumatic injury.
Major Proposed Activities (as written by the applicant)	• To define the highest tolerable dose of subpially injected human cortical stem cells in immunodeficient rats. • To test for disease modifying activity of subpially delivered therapeutic candidate (human cortical stem cells) in rat G93A ALS model. • To characterize the safety of subpially delivered human cortical stem cells in immunosuppressed pigs: a dose escalation study.
Statement of Benefit to California (as written by the applicant)	California leads the nation in supporting stem cell research with the aim of finding cures for major diseases including amyotrophic lateral sclerosis (ALS). A common need to accelerate the clinical translation of these potentially live saving therapies are methods to non-invasively deliver cells into spinal parenchyma. This project aims to meet these challenges by evaluating the treatment effect of a novel spinal cell delivery method and stem cell line in rat ALS model.
Funds Requested	$2,126,070
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: --

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

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

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 the necessary significance and potential for impact?	4	5	5
Is the rationale sound?	1	11	2
Is the proposal well planned and designed?	0	10	4

Is the proposal feasible?	1	7	6

Reviewer Comments

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

Strengths

- Spinal neurodegenerative disorders, including ALS, need new therapeutic options; this proposal offers one possible solution
- Segmental cell delivery may be more effective in targeting a wider area of tissue injury
- Decent performance on previously funded CIRM grants

Concerns

- The approach of multisegmental stem cell delivery for treatment of motor neuron disease is not novel (e.g. Lepore-AC et al., Nat Neurosci. 2008).
- Subpial transplantation is not used by others, but the question of how this would scale to a larger spinal cord is not even considered as an important concern
- There is a great deal of data that indicates astrocytes in ALS are defective in their trophic support and may even secrete toxic substances; the possibility that this would alter the function of transplants is not considered or investigated, yet experiments in such diseased tissue are essential in making a convincing case for the value of a cellular intervention
- Transplantation into healthy tissues is not a model for transplantation into the diseased ALS tissue, which has changes that could limit migration and/or division; thus, extrapolation from the proposed tissue to diseased tissue is not possible
- ALS disease is one of inflammation but model is immunodeficient which does not resemble the diseased state
- Using pre-symptomatic and non-injured animals is a misguided animal model to test the efficacy of segmental cell delivery
- Pig model does not appear to reflect ALS - information will be limited to migration in healthy tissue
- It is unclear how many cells are needed

DISCOVERY

Application #	DISC2-10666
Title (as written by the applicant)	Engineering Live Meniscus Tissue by Electrospinning and Electrospraying Stem Cells
Research Objective (as written by the applicant)	A nano-engineered tissue construct possessing properties comparable to the native meniscus that can reconstruct lost meniscal tissue and can prevent secondary knee osteoarthritis.
Impact (as written by the applicant)	Meniscal injury and surgery is the most common orthopaedic condition affecting over 600,000 every year. We propose to prevent secondary arthritis after meniscal damage.
Major Proposed Activities (as written by the applicant)	• DIFFERENTIATE PLURIPOTENT CELLS INTO MENISCAL PROGENITORS • ENGINEER A BIOMIMETIC SCAFFOLD PROPERTIES OF HUMAN MENISCUS • REPAIR EX VIVO MENISCAL DEFECTS USING LIVE TISSUE-ENGINEERED CONSTRUCTS • DEMONSTRATE EFFICACY OF MENISCAL RECONSTRUCTION IN VIVO
Statement of Benefit to California (as written by the applicant)	A stem cell-based approach for treating meniscal lesions is not represented in CIRM's current Translational Portfolio. This application addresses an unmet medical need that, if successfully developed and made available to patients, will represent a significant improvement upon the current standard of care.
Funds Requested	$1,876,585
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: --

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

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

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 the necessary significance and potential for impact?	6	7	1
Is the rationale sound?	0	10	4
Is the proposal well planned and designed?	1	9	4
Is the proposal feasible?	0	10	4

Reviewer Comments

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

Strengths

- High impact; tears of the meniscal tissue is extremely common and complete or partial removal of the tissue does not solve the problem
- Plan for pre-pre IND meetings and preclinical models proposed for testing of therapeutic candidates are clinically relevant

Concerns

- There are not enough preliminary data to support the hypothesis that the selected cell source and scaffolds will be superior to other tissue-engineered strategies
- There is very little preliminary data and no data to support the generation of pluripotent cell-derived fibrocartilage progenitors and of their supportive scaffolds
- It is somewhat worrying that the team does not yet know what cells they will be using
- It is unclear what characteristics the differentiated cells will display
- Variability of cells in the scaffold is not described
- Not clear if cells will stay at initial location; how will migration be studied
- Previously, the PI stated that cell migration did not occur from the scaffold, but did not show the data; in the revision, cell migration will be analyzed; there is concern that the cells will migrate
- The two treatments that will be tested have not been identified
- Preliminary data to support scaffold choice is underdeveloped
- Fig. 6 shows repair with fat pad; not clear why this is relevant to proposal
- Two animal time points are selected, 2 and 12 weeks; a rough estimate is that this will take at least 48 animals, however 16 are budgeted
- Unclear justification of animal numbers
- Very ambitious plan

DISCOVERY

Application #	DISC2-10473
Title (as written by the applicant)	Homing/Efficacy of a Novel Pluripotent Non-Tumorigenic Human Adult Stem Cells Isolated from Adipose Tissue in Acute Myocardial Infarction Mice Models
Research Objective (as written by the applicant)	Human Muse-AT cells will be isolated from lipoaspirate under severe cellular stress conditions (prolonged collagenase, low temperature, lack of nutrients, hypoxia) followed by SSEA3 cell sorting.
Impact (as written by the applicant)	Using novel human pluripotent non-tumorigenic stem cells with high homing capacity, myocardial regeneration and functional restoration in patients with acute myocardial infarction and heart failure
Major Proposed Activities (as written by the applicant)	• Development of a fast, efficient, highly reproducible technology for isolation/triploblastic differentiation/biological activity of Muse-AT cells that meets Good Tissue Practice requirements • Establishment of male and female SCID and CD1 Acute Myocardial Infarction (AMI) ischemia-reperfusion mouse models with high rate of survival and the generation of biologically active, pluripotent non-tumorigenic GFP-Muse-AT cells • Quantification of infarct size/cardio-physiological parameters changes in male/female AMI SCID and CD1 mice models. Determination optimal dose of i.v. injected Muse-AT cells to improve/revert AMI • Efficacy/safety of Muse-AT cells vs adipose stem cells for cardiomyocyte regeneration/function restoration in AMI mice models; sex-specific effects/immune compromised (SCID) vs immune competent (CD1) • Identification of the mechanisms underlying Muse-AT homing into the infarct heart in AMI mice models through the specific interaction of ligand S1P (damage heart)/the receptor SP1R2 (Muse-AT cells) • Determination of in vivo pharmacokinetics/pharmacodynamics and tissue distribution of Muse-AT cells vs adipose stem cells in male and female SCID and CD1 wild types and AMI mice models
Statement of Benefit to California (as written by the applicant)	Acute myocardial infarction and heart failure are a major health care problem. More than 200,000 Californians suffer a heart attack every year with an estimated annual cost of 40 billion dollars. Extensive cardiac damage ultimately leads to heart failure and death. Heart failure is a main cause of hospitalization in California. Success of this novel Stem Cell therapy will significantly reduce the number of patients with disability or death, improve quality of life and reduce healthcare cost.
Funds Requested	$2,171,244
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: --

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

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

(1-84): Not recommended for funding	15

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 the necessary significance and potential for impact?	5	8	2
Is the rationale sound?	1	12	2
Is the proposal well planned and designed?	0	9	6
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

- Potentially interesting cell type
- Muse cells have been replicated by other independent labs
- The induction by hypoxia and the autologous nature of these cells, combined with the functional benefit are strengths of this proposal
- Autologous therapy; patient's own stem cells would be used

Concerns

- It is not clear whether the proposed cells will integrate - major concern given all the other studies using stem cells
- Injecting cells has a low likelihood it will work based on historical type
- Insufficient preliminary mechanistic data showing that the cells are better than all the other cells which have been used before for treating ischemic heart disease
- Mechanism of improvement in cardiac model unknown
- Proposed experiments will not show mechanisms of action
- The idea that pluripotency is identified by marker expression is a flawed concept in the absence of in vivo teratoma formation; this is in fact a hallmark of pluripotency
- Not enough evidence that these are truly pluripotent stem cells
- It is unclear whether the cells are pluripotent
- The lack of lineage tracing studies showing trans-differentiation of these cells in vivo into cardiac cell lineage is a weakness
- The number of cells administered do not appear to be sufficient to repopulate infarcted region by differentiation
- Sorting on SSEA3 may be a bottleneck in translation to clinic
- Scalability seems an issue
- Women as donors of adipose cells may be limiting
- Four full-time un-named personnel seems high for starting the project off the ground

DISCOVERY

Application #	DISC2-10667
Title (as written by the applicant)	Functional human islet-like organoids (HILOs) as therapy for Type 1 Diabetes
Research Objective (as written by the applicant)	Selection of optimal delivery method for ESC-derived islet-like organoids to maximize functionality and survival and minimize immune/fibrotic reactions upon transplantation into diabetic patients.
Impact (as written by the applicant)	Our proposal will progress the development of an unlimited, reproducible source of human engineered islets for transplantation.
Major Proposed Activities (as written by the applicant)	• Incorporate a "kill switch" into ESC-derived HILOs using inducible Caspase 9 activity • Establish immunogenic status of HILOs in humanized PBMC mice • Identify optimal macro-encapsulation device for HILO transplantation • Identify optimal micro-encapsulation approach for HILO transplantation • Enhance HILO immune suppressor functions via CTLA-4 and PDL-1 overexpression
Statement of Benefit to California (as written by the applicant)	Diabetes affects 3 million people in California. Type 1 diabetes (T1D) is a particular burden as it requires life-long administration of insulin. Allo-transplantation of islets is limited by availability of donor cells. This proposal will progress the development of functional ESC-derived islet-like organoids as an unlimited, reproducible source by selection of optimal delivery method to maximize functionality and minimize immune/fibrotic reactions upon transplantation into diabetic patients.
Funds Requested	$2,491,874
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score:--

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

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

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 the necessary significance and potential for impact?	5	5	2
Is the rationale sound?	1	9	1

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

- Generating functional stem cell-derived insulin-secreting cell products will provide an almost inexhaustible source of cells for replacement therapy in T1D
- Innovative data on beta cell maturation
- HILO are extremely impressive and extremely exciting line of investigation
- The HILO product displays functionality similar to human islets in vitro and in vivo
- HILO product displays superior functionality than stem cell-derived beta cells
- Preliminary data for generation of cells and HILO are supportive of the proposed project

Concerns

- Rationale is missing for examining kill switch; prioritizing activities is needed - kill switch, encapsulation or immunomodulation - all cannot be accomplished in 2 years
- Overambitious: they propose to investigate several strategies for eliminating the need for chronic immunosuppression without any preliminary data to support feasibility; some of the strategies proposed are not immunoisolating and will require immunosuppression
- Too many diverse approaches to engineering the cellular therapeutic
- The rationale for comparing a multitude of very different immunoisolating devices is not explained nor supported by preliminary data
- Rationale is missing for testing two subcutaneous and one omental encapsulation device- this alone is the focus of 5 year grants
- There are no preliminary data for any combination of immunoisolating strategy and HILO; the investigators should focus on testing one product first and based on preliminary results decide how to move forward
- There is limited data on clinical translation of the combination product
- The CTLA4-IG and PDL1 approach is sufficient for a grant in its own right
- Lack of consideration of alternatives for each strategy shows limited depth of investigation

DISCOVERY

Application #	DISC2-10556
Title (as written by the applicant)	Promoting myelin repair in Multiple Sclerosis via N-acetylglucosamine induced oligodendrocyte differentiation from neural stem/progenitor cells.
Research Objective (as written by the applicant)	Evaluate the ability of the simple sugar and dietary supplement N-acetylglucosamine in promoting myelin repair from endogenous stem cells.
Impact (as written by the applicant)	Progressive neurodegeneration in multiple sclerosis (MS) lacks safe effective therapies. N-acetylglucosamine may stimulate endogenous stem cells to promote myelin repair and treat progressive MS.
Major Proposed Activities (as written by the applicant)	• Evaluate the ability of N-acetylglucoasmine in promoting human stem cells to differentiate into myelin forming cells. • Evaluate the ability of N-acetylglucoasmine in promoting myelin repair in mouse models of Multiple Sclerosis.
Statement of Benefit to California (as written by the applicant)	There is a great need for effective and safe treatments of progressive Multiple Sclerosis. N-acetylglucosamine is currently in an early stage clinical trial in MS to assess a role in inflammation. Positive results from the proposed new studies would re-direct a future Phase 2 clinical trial of N-acetylglucosamine to assess progressive MS and myelin repair. Such a trial would be based in California and success would provide a novel and safe therapy for Californians suffering from MS.
Funds Requested	$939,160
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: --

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

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

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 the necessary significance and potential for impact?	5	7	3
Is the rationale sound?	0	13	2
Is the proposal well planned and designed?	0	9	5
Is the proposal feasible?	1	9	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

- N-acetylglucosamine (GlcNAc) is in wide use for MS and other conditions, as individuals use it without prescription as a nutraceutical; it is very important to do research on such compounds to further inform such use
- The molecular biological mechanism of action hypothesized is very well thought out, insightful, and thoroughly described
- MS is a high priority

Concerns

- A phase 1 clinical trial is currently being undertaken; rationale for these proposed studies in the perspective of the phase 1 is not clear
- It is unclear what the rationale is for this study, and what caveats from the phase 1 trial that they would like to address
- Findings will not influence therapy
- The connection of the proposal to translational science seems to be that these experiments will help plan a phase 2 trial, however, exactly how the outcome would inform such a plan is very unclear
- Preliminary data suggest that levels of GlcNac required to influence differentiation are not attainable in vivo, and prenatal treatment relevance is unclear
- There may be other possible molecular biological mechanisms of action
- Myelin regeneration is surely important for relapsing-remitting MS as well as primary progressive MS, so GlcNac would be expected to work for both

Recommendations

- The worldwide sales of GlcNAc in dollars would be useful to include
- It would be good to describe alternative hypotheses for possible mechanisms of action and test one of these

DISCOVERY

Application #	DISC2-10709
Title (as written by the applicant)	Novel anti-arrhythmic agents in cardiac cell-based therapy
Research Objective (as written by the applicant)	We propose to use a novel lead compound to increase the survival and engraftment of transplanted cardiac stem cells by reducing inflammation in the host myocardium.
Impact (as written by the applicant)	Current stem cell therapy for heart failure has not produced full restorative functions. We propose to increase the survival of the transplanted stem cells by reducing inflammation using a novel drug.
Major Proposed Activities (as written by the applicant)	• Develop and select a lead candidate that is orally available and test the efficacy, dosing, and safety profiles to be used with stem cell transplantation in a preclinical model. • Transplant cardiac stem cells in preclinical models and treat with the lead compound to enhance stem cell survival and retention and reduce cardiac arrhythmias with short and long term follow up. • Determine the mechanisms of action for the prevention of cardiac arrhythmia and the anti-inflammatory property of the lead compound. • Determine the mechanisms of action in the prevention of cardiac arrhythmia and the anti-inflammatory property of the lead compound. • Comprehensive analyses of safety profiles and dosing to demonstrate the potential use of the lead compound in combination with cardiac stem cell in humans.
Statement of Benefit to California (as written by the applicant)	Cardiovascular disease remains the leading cause of death in California and is responsible for more deaths than all cancers combined. Current cardiac stem cell therapy to combat heart failure has not produced full restorative functions. A high rate of transplanted stem-cell loss has been observed due to ischemia and inflammation in the host environment. Our study will address this major setback in the current cardiac stem cell therapies.
Funds Requested	$2,200,800
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: --

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

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

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 the necessary significance and potential for impact?	3	8	1
Is the rationale sound?	0	11	1
Is the proposal well planned and designed?	0	8	4
Is the proposal feasible?	0	9	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 anti-inflammatory drug in question is apparently very efficacious
- The PI is established and the environment is excellent

Concerns

- There is only a moderate likelihood that the proposed treatment will advance the field; in the revised application there is a lack of convincing evidence that the proposed mechanisms has a substantial impact on the proposed disease phenotype
- The proposal does not sufficiently address concerns related to the underlying question whether the proposed mechanism is sufficiently relevant and the pathway targeted by the proposed drug is a good candidate
- The rationale for trying to fit the drug as a regenerative therapy is still not sufficient
- The preliminary data support parts of the overall underlying hypothesis; however there is still limited data supporting the notion that the proposed mode of action contributes substantially to the overall problem, namely arrhythmia and the retention of cells in the heart
- The main concern is that validation for the use of this drug remains unconvincing; many aspects are not addressed such as other mechanisms of arrhythmias secondary to myocyte injection not related to inflammation, rationale for this drug instead of another anti-inflammatory strategy
- The preliminary data describing the effect in a horse lacks the necessary scientific rigor to describe scientific evidence: this relates to sample size, dose of drug, effect, timelines, treatment regimen, control group, etc...
- It is unclear why sEHI pre-treatment of cells is not done- what is the rationale of 3 weeks treatment when the cytokine storm/inflammation is upon administration, i.e. first 24 hours
- The rationale for the selection of the rabbit model is unclear - the porcine model is more physiologically relevant to humans

DISCOVERY

Application #	DISC2-10421
Title (as written by the applicant)	SEMA4D as a predictive biomarker for brain metastasis
Research Objective (as written by the applicant)	Develop a blood sample based approach to predict the likelihood of brain metastasis for patients with breast and lung cancers using a candidate biomarker SEMA4D
Impact (as written by the applicant)	Currently there is no means to predict brain metastasis for cancer patients. This research will fill this void with a predictive biomarker for brain metastasis using blood samples from patients.
Major Proposed Activities (as written by the applicant)	• Evaluating cancer subtypes that are impacted by SEMA4D in promoting tumor cells crossing from blood to brain barrier • In vivo prospective analysis of cancer subtypes for the potential of SEMA4D in promoting brain metastasis in mouse models • Effect of blocking SEMA4D signaling on brain metastasis using brain metastasis-forming circulating tumor cell (CTC) lines • Association of SEMA4D expression level in CTCs with brain metastasis from breast and lung cancer patients with or without brain metastasis • Association of SEMA4D genomic amplification in CTCs with brain metastasis from breast and lung cancer patients with or without brain metastasis • Association of cleaved SEMA4D level in the plasma of the blood samples with brain metastasis from breast and lung cancer patients with or without brain metastasis
Statement of Benefit to California (as written by the applicant)	Brain metastasis is a major public health problem. It is the most common intracranial malignancy, affecting approximately 200,000 new patients annually in the United States and accounts for significant morbidity and mortality in cancer patients. The prognosis for brain metastasis is devastating and there is no predictive measure. Our proposed research aims to develop a novel blood based predictive measure that can have a significant impact on this huge unmet need in cancer patients.
Funds Requested	$1,077,764
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: --

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

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

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 the necessary significance and potential for impact?	3	9	2
Is the rationale sound?	1	8	5
Is the proposal well planned and designed?	2	10	2
Is the proposal feasible?	1	9	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

- Brain metastasis is an important clinical problem
- Better understanding the cause of brain metastases and how to prevent them could be of significant medical importance
- The overall objective offers a sound rationale to develop SEMA4D expression in CTC as a predictive diagnostic marker for metastasis
- If the biomarker is validated, patients can be monitored to detect brain metastasis in earlier stages allowing stratification of patients for more aggressive preventive interventions
- The team of experts assembled is very appropriate to run this project; investigators have extensive experience working in the field of circulating tumor cells and metastasis as well as developing new technology for the detection of cancer cells in the peripheral blood

Concerns

- The development of a biomarker for brain metastasis has unclear clinical utility, i.e., what would be done with this information
- It is unclear how this project will impact on patient care
- It is unclear what one would do if CTC analysis showed more SEMA4D cells
    - The evidence for the benefit of increasingly aggressive treatments of cancers at such a late stage is not clear
    - Patients clearly have a decreased quality of life from many of the aggressive treatments
- Strategies to prevent CNS metastases would be important, but this is not addressed by the application
- The in vitro blood brain barrier work is intriguing but is not a surrogate for generation of brain metastasis
- It is unclear why investigators did not use melanoma models as melanoma patients have the highest propensity of brain metastasis
- It is unclear whether this project is a diagnostic or therapeutic tool
- The hypothesis that SEMA4D expression actually increases brain metastases is not tested, nor is the question of whether blocking SEMA4D would prevent brain metastases
- This grant proposes isolation of CTC from blood samples of breast or lung cancer patients and perform analysis on these samples:
    - Yield of CTC from patients who have already had a primary tumor will vary depending on the time when the blood is drawn from the patients
    - The methodological details about this aspect of the study are not very clear
- There is no IRB assurance that clinical specimens can be collected
- There are no statistical justifications that would generate a sample size for the biomarker studies
- Pathway to validation not clear

DISCOVERY

Application #	DISC2-10441
Title (as written by the applicant)	Novel Tools for Drug Discovery: Generation of Hematopoietic Stem and Progenitor Cells from Primary Human Leukemia-derived iPSCs
Research Objective (as written by the applicant)	We will make iPSC from leukemic cells from patient bone marrow and blood. Hematopoietic stem/progenitor cells (HPSC) that have key attributes of the patient's cells will be derived from these iPSC.
Impact (as written by the applicant)	Primary leukemic cells are needed to evaluate new drugs but very few samples are commercially available. Leukemic HSPC derived from our iPSCs will be valuable tools to accelerate new drug development.
Major Proposed Activities (as written by the applicant)	• iPSC lines will be made from CD34+ cells from AML and CML bone marrow or ALL and CLL peripheral blood. These iPSC lines will be evaluated for expansion potential and initial cell banks will be made. • Leukemic iPSC lines will be tested for pluripotency markers, karyotype, and key mutations of the parent leukemic population. Ig gene rearrangements will be determined for B-ALL and CLL derived lines. • Using iPSC generated from normal CD34 cells, differentiation cultures will be optimized to generate blood stem and progenitor cells from iPSC and assays to characterize them will also be established • HSPC from leukemia-derived iPSC lines will be generated and characterized to see if they retained the key biological attributes of the original primary leukemia.
Statement of Benefit to California (as written by the applicant)	With over 1500 biotech companies in our state developing drugs for intractable diseases, our iPSC tools will accelerate drug development for diseases like AML, where the 5-year survival rate is only 27%. Our tools will help biotechs develop more effective drugs for leukemias faster. These novel drugs will directly help the 120,000 Californians with living with leukemia and lymphoma. And, approved drug manufacturing and sales will contribute to business growth in many sectors of our economy.
Funds Requested	$587,672
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: --

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

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

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 the necessary significance and potential for impact?	2	9	3
Is the rationale sound?	0	9	5
Is the proposal well planned and designed?	0	9	5
Is the proposal feasible?	0	9	5

Reviewer Comments

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

Strengths

- A renewable source of tumor cells may be useful scientifically
- A source of more leukemia cells (esp AML) would be useful
- Leukemic lines may be useful for insights gained on driving mechanisms
- Generating a large pool of iPSCs from several types of leukemia is innovative
- Learning more about how to make iPSCs from leukemia is an interesting challenge
- The proposed work is based on recent publications, as such it is very scientifically sound
- The team appears to have the necessary expertise to carry out the work
- Team is excellent

Concerns

- The proposed aims represent an important starting point, but fall short of addressing whether the team is able to recreate the generation of leukemic cell lines
- Although it was recently published that AML and other leukemic cells can be made into iPSCs, there are still additional bottlenecks not addressed in the application, like the efficiency of PSC to HSC differentiation
- The preliminary data are underwhelming, as there is a noted difficulty in the generation of iPSC from ALLs, and low efficiency in AML-derived iPSCs
- Feasibility is questionable based on preliminary data
- Focusing on one type of leukemia (AML) is suggested
- May be best to focus on AML as the preliminary data is on AML
- It is likely that different protocols would be required for different types of tumor cells
- The steps to ensure fidelity with the original tumor were not entirely convincing
- No evidence is presented to support the notion that the leukemia-derived iPSCs will in fact recreate the leukemic state
- The functional testing of the leukemic outcomes remains cumbersome

DISCOVERY

Application #	DISC2-10729
Title (as written by the applicant)	Manipulation of oxygen and pressure to increase neural cell differentiation efficiency and promote functional maturation
Research Objective (as written by the applicant)	This project aims to produce a culture system that uses microenvironmental control to more efficiently produce functionally mature neural cell subtypes from IPSCs or neural precursor cells.
Impact (as written by the applicant)	This system would greatly increase the number of neural cell model systems that could be used for discovery purposes, as well as decrease the time and resources required to generate each model .
Major Proposed Activities (as written by the applicant)	• Develop and identify methods/conditions to optimize generation of functionally mature neural cells from NPCs using control of oxygen and pressure in conjunction with standard maturation protocols. • Expand on our preliminary findings by testing six to twelve additional neural precursor cell lines to understand the reproducibility of improving the efficiency and cell quality in neural maturation. • Perform analysis aimed at elucidating mechanism of action for how oxygen and pressure can allow for efficient generation of mature cells. • Develop a Target Product Profile that can form the basis of future translational development of the tool that will be a source of information for expected outcomes and range of performance.
Statement of Benefit to California (as written by the applicant)	The understanding of diseases and the future of cell therapy depend on the ability to reliably and efficiently generate a variety of fully functional cell types. This tool offers a novel approach to generate functionally mature neural cell types that can serve as models for genetic and aging related diseases suffered by Californians. The approach proposes to improve the cell quality generated from stem cells with workflows that reduce the amount of time and reagents required.
Funds Requested	$698,400
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: --

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

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

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 the necessary significance and potential for impact?	1	10	3
Is the rationale sound?	1	11	2
Is the proposal well planned and designed?	0	12	2
Is the proposal feasible?	0	11	3

Reviewer Comments

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

Strengths

- Confirms oxygen role in cell culture environment
- Strong basic science

Concerns

- There is little innovation or new proposed here
- Translational aspects are missing: it is unclear what the technology is
- Avatar technology can be employed in current cell incubators, thus the significant technological advance here is not apparent
- Neural differentiation is not that problematic
- Preliminary data do not reflect adequate controls
- Preliminary data unconvincing; oxygen control is not novel and there is no basis for studies of pressure