TOTAL BUDGET: DISC 1 2017	
TIER 1	$1,367,078
TIER 2	$6,964,695

Application Number	Title	Score	Mean	SD	Low	High	Budget	T1	T2	Tier
DISC1-10074	Reprogramming human stem cells for blood cell generation	90	90	0	90	90	$232,200	13	0	1
DISC1-10036	Prodrug innovation to target muscle stem cells and enhance muscle regeneration	86	87	2	85	90	$235,834	12	0	1
DISC1-10079	An exosome-based translational strategy to mitigate Alzheimer's disease neuropathology	85	86	2	85	89	$179,911	14	0	1
DISC1-09912	A Novel Tissue Engineering Technique to Repair Degenerated Retina	85	86	2	85	90	$215,133	14	0	1
DISC1-09999	Generation of expandable, self-renewing muscle stem cells for Duchenne Muscular Dystrophy	85	85	2	80	88	$265,500	9	5	1
DISC1-09984	Hypo-immunogenic cardiac patches for myocardial regeneration	85	85	2	80	88	$238,500	13	1	1
DISC1-09991	Development of dual-gate chimeric antigen receptor therapy for lethal, stem-like neuroendocrine prostate cancer	82	82	4	75	90	$221,858	6	8	2
DISC1-09812	Development of hESC-derived cardiomyocyte/fibroblast aggregates for optimal cell transplantation	80	81	2	80	85	$230,400	2	12	2
DISC1-09843	Leveraging post-transcriptional gene regulation to expand hematopoietic stem cells	80	79	5	70	86	$243,000	4	10	2
DISC1-09922	Development of treatments to improve healing of ischemic wounds	80	79	3	75	85	$235,800	2	12	2
DISC1-09957	Development of a Pleiotrophin Monoclonal Antibody to Reduce Leukemic Stem Cell Growth	80	78	5	65	80	$230,400	0	13	2
DISC1-09891	High-throughput analyses of drivers of neural stem cell differentiation	76	78	4	75	85	$230,400	1	13	2
DISC1-09970	Prevention of the metastasis through cancer stem cell-specific targeting using nanomedicine	79	77	4	70	80	$235,800	0	14	2
DISC1-10001	Induction of immune tolerance of hESC-derived allografts using HLA-matched hESC-derived immune suppressive dendritic cells	75	77	2	75	80	$232,200	0	14	2
DISC1-09976	Anti-inflammatory mesenchymal stem cells 2 (MSC2) as a disease-modifying therapy for Huntington's disease	75	74	8	60	90	$301,266	2	12	2
DISC1-10014	Human Pancreatic Cancer Stem Cells: A Novel Way for Eradication	75	74	4	70	85	$303,894	1	13	2
DISC1-10076	Transient gene activations for improved stem cell differentiation to endoderm and mature Human Hepatocytes	70	73	5	70	85	$149,999	1	13	2
DISC1-10096	Characterization of hCD47b mAb Anti-Melanoma Properties in the Immune-Humanized Mouse Model	73	73	2	70	75	$202,680	0	13	2

Application Number	Title	Score	Mean	SD	Low	High	Budget	T1	T2	Tier
DISC1-09949	Human pluripotent stem cell-derived satellite-like cells for skeletal muscle regeneration	75	72	10	45	80	$148,500	0	13	2
DISC1-09989	Development of epigenome-editing biologics for stem cell fate specification	70	71	6	65	84	$223,204	0	13	2
DISC1-09931	Validation of a human induced pluripotent stem cell derived neuromuscular co-culture platform for disease modeling and drug discovery	70	70	1	70	73	$204,187	0	13	2
DISC1-09807	Engineering Cell-Cell and Cell-Matrix Interactions to Optimize the Differentiation of hiPSC-Derived Cardiac Myocytes	70	70	0	70	70	$238,585	0	14	2
DISC1-09956	Opposing roles of Cerberus1 and Gremlin1 in hESC exit from pluripotency	70	70	0	70	70	$232,200	0	12	2
DISC1-09973	Human Pancreatic Beta-Cell Regeneration by Islet Cell Transdifferentation	70	70	0	70	70	$265,500	0	14	2
DISC1-09895	Artificial Intelligence Approach to Directed Differentiation of Human Pluripotent Stem Cells	70	70	5	60	75	$150,000	0	14	2
DISC1-10058	Integrated approach for combined in situ gene and stem cell based therapy for urea-cycle disorders	70	68	8	50	80	$232,200	0	14	2
DISC1-09960	Reversion of Cellular Hallmarks of Aging through Transient Somatic Reprogramming	65	67	9	50	85	$230,453	1	12	2
DISC1-09990	Direct in vivo reprogramming of organism native differentiated tissue into precursors of the same lineage as a novel safe regenerative paradigm.	65	66	6	60	80	$235,800	0	14	2
DISC1-09923	Exploring mechanisms controlling proximal-distal progenitor cell fate in the human lung	65	65	6	50	70	$210,627	0	14	2
DISC1-10071	Functionalized Nanoparticles in Direct Reprogramming of Human Fibroblasts to Functional Hepatocytes	60	60	5	45	70	$150,000	0	14	2
DISC1-09994	Zika Virus-induced Disturbances in Human Neural Stem Cell Mitosis and Migration: Role of Centrosomes and Microtubules	60	59	10	30	82	$241,992	0	14	2
DISC1-10020	Identification of Human Spermatogonial Stem Cell-Specific Markers	60	59	9	30	75	$232,200	0	14	2
DISC1-09870	Purine-PSEN1 interaction in a hiPSC model of Alzheimer’s disease	--	--	--	--	--	$232,200	0	13	2
DISC1-09978	Effects of Human Neural Progenitor Cells on Chronic Pain Outcomes after Severe Spinal Cord Injury	--	--	--	--	--	$232,200	0	14	2
DISC1-10087	Therapeutic potential of human umbilical cord derived mesenchymal stem cells in neonatal bronchopulmonary dysplasia	--	--	--	--	--	$202,680	0	13	2
DISC1-10017	Modeling Zika viral infection and congenital Zika syndrome in human neural stem cells	--	--	--	--	--	$250,200	0	13	2
DISC1-09830	Development and validation of a computational prediction model for exogenous neural stem cell migration in the brain	--	--	--	--	--	$234,270	0	14	2

DISCOVERY

Application #	DISC1-09807
Title (as written by the applicant)	Engineering Cell-Cell and Cell-Matrix Interactions to Optimize the Differentiation of hiPSC-Derived Cardiac Myocytes
Research Objective (as written by the applicant)	Use microfabrication techniques to determine how select cell-matrix and cell-cell interactions impact the differentiation of functional cardiac myocytes from human induced pluripotent stem cells
Impact (as written by the applicant)	If successful, this research will improve the manufacturing of cardiac myocytes from induced pluripotent stem cells for applications in regenerating new heart muscle and drug screening
Major Proposed Activities (as written by the applicant)	• Engineer defined cellular microcompartments to optimize the transcriptional, structural, and functional differentiation of hiPSC-derived cardiac myocytes • Determine the impact of cardiac fibroblasts and fibroblast-derived extracellular matrix on the structural and functional maturation of hiPSC-derived cardiac myocytes
Statement of Benefit to California (as written by the applicant)	Our research will improve the process of manufacturing cardiac myocytes from pluripotent stem cells. Cardiovascular disease is the leading cause of death in California. Thus, there is a critical need to efficiently and robustly manufacture cardiac myocytes from pluripotent stem cells to regenerate new myocardium and to build in vitro models for studying diseases and screening drugs. Our research will directly contribute to this need, with the long-term goal of benefiting patients.
Funds Requested	$238,585
GWG Recommendation	***Not recommended for funding***

Total Scoring Data

Final Total Score: 70

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

Mean	70
Median	70
Standard Deviation	0
Highest	70
Lowest	70
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (1-84): Not recommended for funding	14

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	1	0	2

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

Reviewer Comments

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

Strengths

- The lack of mature phenotypes represents a translational roadblock for iPSC-derived cardiomyocytes. The investigator proposes engineering tools for optimization of culture conditions and for validation of maturation of cardiomyocytes through unique functional readouts.
- The PI has expertise on the specific model.
- The approach of co-culturing cardiomyocytes with cardiac fibroblasts on micropatterned substrates and determining the mechanisms (ECM or paracrine mediated) is novel.
- The project is well-designed to test the hypotheses that matrix mechanics and fibroblast interactions affect iPSC differentiation to cardiomyocytes.
- The PI has expertise with the tools and strong preliminary data indicating feasibility of the project.
- The quantitative, engineering approach is strong and the project focuses on electromechanical phenotypes of the cardiomyocytes.

Concerns

- The novelty and innovation are low. There are numerous studies demonstrating effects of matrix mechanics and fibroblasts and other stromal cells on iPSC-CM differentiation and function. The proposed study is better designed than many of these, but added value would be incremental.
- The lack of novelty in the approach is the primary concern. Several groups have pursued very similar strategies with only incremental gain.
- Prior studies in this area have had relatively small impacts on maturity.
- The proposed platform is applicable only for disease modeling because of scalability issues that will prevent its utilization for regenerative medicine approaches.
- The preliminary data using human iPSCs are qualitative. The only quantitative data provided are using mature rat neonatal cardiomyocytes.
- A schematic or table indicating the different experimental variables that will be investigated is missing.

DISCOVERY

Application #	DISC1-09812
Title (as written by the applicant)	Development of hESC-derived cardiomyocyte/fibroblast aggregates for optimal cell transplantation
Research Objective (as written by the applicant)	Our objective is to generate aggregates consisting of hESC-derived cardiac fibroblasts and cardiomyocytes in a natural extracellular matrix to promote viability and integration after transplantation.
Impact (as written by the applicant)	The inclusion of supportive cells, such as fibroblasts, for transplantation will significantly improve the viability and engraftment of hESC-derived cardiomyocytes.
Major Proposed Activities (as written by the applicant)	• Differentiation of a MESP1 hESC-reporter line to isolate cardiac-specific fibroblasts • In vitro characterization and gene expression analysis of the hESC-derived cardiac fibroblasts • Developing a culture system to form 3D aggregates of cardiomyocytes dispersed throughout a network of cardiac fibroblasts • Determining the effect of co-culture of fibroblasts on cardiomyocyte expansion and maturation • Examining the survival and engraftment of the 3D aggregates of hESC-derived cardiac fibroblasts and cardiomyocytes in a small animal model
Statement of Benefit to California (as written by the applicant)	In California, more than 70,000 people die every year from cardiovascular diseases. Human embryonic stem cells (hESCs) could offer a therapeutic option for patients with damaged heart. We propose to isolate fibroblasts and cardiomyocytes from hESCs and culture them in a natural matrix prior to transplantation. This approach will improve the viability and engraftment of the transplanted cells. We expect that California health care entities will be first in line for trials and therapies.
Funds Requested	$230,400
GWG Recommendation	***Not recommended for funding***

Total Scoring Data

Final Total Score: 80

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

Mean	81
Median	80
Standard Deviation	2
Highest	85
Lowest	80
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	2
Tier 2 (1-84): Not recommended for funding	12

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	10	1	3
Is the rationale sound?	7	1	6
Is the proposal well planned and designed?	3	5	6
Is the proposal feasible?	2	6	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 rationale for generating cardiac fibroblasts (CF) from hPSCs to improve cardiomyocyte function and engraftment is sound.
- The ability to efficiently produce fibroblasts from hPSC-derived cardiac progenitors would represent a significant advance and enable subsequent studies on the impact of these cells in translational applications.
- The research team is outstanding and has significant expertise in developing stem cell-derived therapeutics for cardiovascular disorders.
- MESP1 cell line is in place and will facilitate understanding what cues drive fibroblast differentiation from these progenitors.
- RNAseq comparison of hESC-derived CFs with in vivo CFs is a strength.
- Aim 3 is strong, although by only looking at 8 weeks post transplantation there are concerns cell survival will be low.
- The availability of the MESP-1 reporter hESC line previously developed by the PI, which is a critical tool to optimize ES differentiation, is a strength of the proposal.
- The rationale that additional signals are necessary for promoting viability and engraftment of transplanted cardiomyocytes and that large cardiomyocyte/fibroblast clusters display enhanced survival is strong.
- The proposal includes a great discussion of potential pitfalls and alternative strategies.
- The PI’s background and environment are strong for clinical translation.

Concerns

- Fibroblasts are very difficult to define. Markers alone are insufficient. Functional analyses would strengthen the proposal.
- Cardiac fibroblasts are very poorly defined and there are no clear functional parameters defined by which to characterize the cells or their successful derivation.
- The PI's work has shown that most fibroblasts come from the epicardium. Other labs have generated cardiac fibroblasts from hESC-derived epicardial cells. It isn't clear why those fibroblasts are not sufficient for the applications proposed.
- There is no clear rationale for the specific factors used to drive fibroblast differentiation from MESP1+ cells.
- There is concern that the proliferative fibroblasts will outcompete the non-proliferative cardiomyocytes during long-term organoid culture.
- Additional functional characterization of cardiomyocyte maturation (Aim 2) beyond decreased proliferation and electrophysiology will be important.
- The lack of proposed experiments to determine whether engrafted cells are truly functional in integrating with host tissue and restoring cardiac function after transplantation is a concern.
- Some of the images provided in the proposal are at poor resolution and hard to read.
- The strategy for high throughput screening of media supplements for promoting differentiation of cardiac fibroblasts (Aim 1a) is not outlined.

- No preliminary data are provided to support functional characterization of differentiated cells (Aim 2b).
- The proposal lacks adequate description of the different experimental conditions (ratio of cardiac fibroblasts to cardiomyoctes).
- Completing the study in one year seems unrealistic. Differentiation process optimization takes a long time, and Aims 2 and 3 cannot progress until a process is locked in.

DISCOVERY

Application #	DISC1-09830
Title (as written by the applicant)	Development and validation of a computational prediction model for exogenous neural stem cell migration in the brain
Research Objective (as written by the applicant)	We will develop a method to understand neural stem cell migration in the brain based on tissue orientation and to predict most likely routes that therapeutic stem cells will take to the target sites.
Impact (as written by the applicant)	Successful application could be used to identify patients that are good candidates for neural stem cell therapy depending on their tumor's location and to design the best administration method.
Major Proposed Activities (as written by the applicant)	• To develop a method of NSC migration in the brain based on tissue orientation and validate in preclinical studies
Statement of Benefit to California (as written by the applicant)	Successful application of this approach will provide a way to predict the numbers of therapeutic neural stem cells (NSC) that will reach a tumor depending on the dose, route of delivery, and location of a tumor. This tool may be used to design the best administration method of NSCs, which will provide a personalized medicine approach of NSC therapy and directly benefit patients in California. The use of this tool in clinical trials will attract national attention to the State of California.
Funds Requested	$234,270
GWG Recommendation	***Not recommended for funding***

Total Scoring Data

Final Total Score: --

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

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

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	0	0	1

Is the rationale sound?	0	0	1
Is the proposal well planned and designed?	0	0	1
Is the proposal feasible?	0	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

- An improved understanding of stem cell distribution in the brain would be valuable for designing strategies to treat brain tumors.
- The approach to mathematically model NSC migration through brain tissue based on brain structure is very innovative.
- The proposed experimental plan is straightforward and clear, all resources are in place to develop and validate the model.
- This is an excellent multidisciplinary team with expertise in modeling cell migration and developing stem cell therapies to treat brain tumors.

Concerns

- The assumption that cell distribution is solely controlled by tissue structure may be an oversimplification.
- Clinically, NSCs would be injected into the tumor and the tumor would alter the architecture of the brain. The model doesn't seem to account for this.
- It is difficult to see how this model could be adapted to designing patient-specific treatments. At the level of detail described, the model appears to be descriptive rather than predictive.
- There is not enough indication that the treatment or the analysis is of value.
- The NSC transplants seem to home to a large tumor mass, which is surgically removable. Evidence for tracking small numbers of cells is unclear.
- The impact seems limited to the specific case of predicting migration paths of neural stem cells in situations where there is enough data to predict tissue anisotropy but not enough data to fully map white matter.
- A good computational model - given the complexity of tropism - will require a lot of data. So much data, in fact, that the model will likely be good only at 'predicting' paths already in the training data. To be useful, a computational model would have to predict paths of cells with different properties than those it was trained on. But the complexity of the system is so vast, it is doubtful that such extrapolation is possible. Testing the model in animals is not likely to provide relevant training data in humans.
- Developing a computational model that made good predictions of novel behaviour in an animal model would provide confidence in the general approach.
- The voxel with both the greatest coherence and minimum difference in orientation is chosen as the next step in the migration path. Presumably, there are cases where the voxel with the greatest coherence does not have the minimum difference in orientation. Does the path then stop?
- How does a stem cell know how long a path is before it starts its migration? And if it doesn't, how does it know to take the shortest path? Wouldn't it choose a path based on local signals and continue to follow that path? One supposes it might turn around in sort of a brownian motion on a longer path, before it reached a collector state, and so a shorter path might be more likely. But that does not seem to be the hypothesis of this proposal.
- It is not clear that there is a difference between "migration along white matter paths" and "migration along coherence paths" as in the human brain. The investigator alludes to this stating a hypothesis of migration along white matter. It would seem that a prediction that stem cells migrate along white matter is equivalent to the mathematical formulation provided and explored here. This seems like a very long way to go to formulate a simple hypothesis.

DISCOVERY

Application #	DISC1-09843
Title (as written by the applicant)	Leveraging post-transcriptional gene regulation to expand hematopoietic stem cells
Research Objective (as written by the applicant)	Using our recent discoveries in basic mechanisms of gene expression, we seek to develop new ways to expand blood stem cells.
Impact (as written by the applicant)	We will be able to increase the number of blood stem cells available for transplantation, increasing the number of patients we can treat. It will also help guide new research in this area.
Major Proposed Activities (as written by the applicant)	• First, we seek to define whether the protein we discovered can increase numbers of human blood stem cells, and whether they maintain their properties of being able to produce all types of blood cells. • Second, we seek to discover ways that can cause an increase in the protein we discovered, with the aim of developing pharmaceutical or other products in the future to expand blood stem cells.
Statement of Benefit to California (as written by the applicant)	Approximately 2,000 blood stem cell transplants were performed per year in California between 2009-2013. This is a fraction of the number of patients who could benefit from such stem-cell based therapy. If we are successful in our project, we can increase the number of deliverable blood stem cells and greatly increase access to this most successful of stem cell treatments to Californians who stand to benefit from this treatment.
Funds Requested	$243,000
GWG Recommendation	***Not recommended for funding***

Total Scoring Data

Final Total Score: 80

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

Mean	79
Median	80
Standard Deviation	5
Highest	86
Lowest	70
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	4
Tier 2 (1-84): Not recommended for funding	10

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	4	3	7
Is the rationale sound?	6	1	7
Is the proposal well planned and designed?	1	1	12
Is the proposal feasible?	3	1	10

Reviewer Comments

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

Strengths

- The PI and colleagues have discovered a protein that appears to act at the post-transcriptional level to expand HSCs. This is potentially a new molecular mechanism that is distinct from current efforts aimed at HSC expansion for transplantation.
- Overall, the proposal has a sound rationale and good experimental plan.
- The PI and research team have the expertise to conduct project.
- The PI is experienced and well-regarded.
- The resources at the research institution are excellent.

Concerns

- The stated need for HSC expansion is not fully justified. It is not clear that the major limitation of transplantation is the relatively low numbers of HSC.
- The examination of the discovered protein may provide insights into HSC and stem cell biology, but the potential that these findings can be applied clinically is relatively low.
- The studies in Aim 1 are feasible, but less so in Aim 2.
- The impact of overexpression of the discovered protein provides mild improvements in engraftment. In addition, this mild effect occurs at a dramatic level of over expression that is unlikely to be achieved through the proposed screening strategy.
- The impact of this project is uncertain. The effect of over expression of the discovered protein *in vivo* is mild. It is not necessarily true that because an effect is observed in vivo that this will also apply to in vitro HSC expansion.
- Information is lacking about expression of the discovered protein, for example, whether it is restricted to HSCs in the adult and during hematopoietic development. If the protein is expressed in the fetal liver, experiments involving the use of Vav-Cre mice may not be feasible as deletion of the protein in Vav+ cells may lead to embryonic lethality.
- The proposal contains grammatical/formatting mistakes.

DISCOVERY

Application #	DISC1-09870
Title (as written by the applicant)	Purine-PSEN1 interaction in a hiPSC model of Alzheimer's disease
Research Objective (as written by the applicant)	Study how altered purinergic signaling, a potential novel pathway in Alzheimer's etiology, might contribute by causing or interacting with the established amyloid- and tau-related disease mechanisms.
Impact (as written by the applicant)	This study could reveal new potential targets for therapeutic intervention in Alzheimer's disease; at the molecular level via purinergic pathways, and at the cellular level in astrocyte contribution.
Major Proposed Activities (as written by the applicant)	• Gene editing to create cell lines that genetically only differ in in either the purinergic or Alzheimer's mutation, or both. So we can directly compare the consequences of the individual mutations. • We will differentiate these cells into neurons and astrocytes to investigate how the mutations affect cellular function and interaction, for example to look at neural network formation and signaling. • We will also look at the molecular level, by studying how these mutations affect gene expression levels in the purinergic signaling and Alzheimer's disease associated pathways.
Statement of Benefit to California (as written by the applicant)	Alzheimer's disease is the leading cause of dementia, and a rapidly growing health concern in aging populations. This study could bring forth potential new targets for treatment, which are sorely needed. Any new therapeutics developed in future studies inspired by these findings, would benefit Californians, Americans and world citizens suffering from the disease alike. The race is on to find a cure, California could be a part of the effort.
Funds Requested	$232,200
GWG Recommendation	***Not recommended for funding***

Total Scoring Data

Final Total Score: --

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

Mean	--
Median	--
Standard Deviation	--
Highest	--
Lowest	--
Count	13
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (1-84): Not recommended for funding	13

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

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

- Interesting hypothesis. It is important to explore causality of Alzheimer's disease (AD) beyond the amyloid hypothesis.
- The proposal recognizes the importance of a new approach to understanding the pathogenesis of AD.
- The proposal to look at astrocyte biology in AD modeling has merit.
- The idea of looking at astrocytes and purinergic signaling is interesting and could provide some useful new information.

Concerns

- The links between purine metabolism and function in Lesch-Nyhan syndrome and AD are not well-articulated.
- Loss of HPRT disrupts a number of aspects of neural differentiation and function. It is not surprising that expression of some AD related genes is altered in LN syndrome.
- There is no evidence that patients with LN syndrome show AD pathology, even those with variant mild forms of HPRT deficiency who live longer.
- Postmortem changes in AD brains may be secondary and may not reflect alterations in early stages of pathogenesis; thus examination of end stage disease may not be informative.
- The fact that AD is late onset makes it unclear that the information obtained by studying early events *in vitro* will be meaningful.
- LN does not appear to have AD like pathology. Moreover, LN is generally early onset.
- The observation that HPRT disruption affects genes in the KEGG AD "pathway" is fascinating. Note that this is a set of genes, not a pathway. Using this observation as the sole (or major) reason to start a larger study is insufficient. It is unclear how specific this finding is since it is likely that knocking out a fraction of all 20,000 genes could have a similar effect.

DISCOVERY

Application #	DISC1-09891
Title (as written by the applicant)	High-throughput analyses of drivers of neural stem cell differentiation
Research Objective (as written by the applicant)	This proposal describes a system to observe the relationship between external controls and internal changes in gene expression that regulate neural stem cell differentiation in to regenerative cells.
Impact (as written by the applicant)	The proposed research would establish a new technology for understanding stem cell differentiation and create new techniques for improving therapeutic treatment of central nervous system diseases.
Major Proposed Activities (as written by the applicant)	• Identify and monitor core sets of transcription factors and their dynamic activity networks during neural stem cell differentiation towards oligodendrocytes. • Identify combinations of microenvironment cues that direct neural stem cell fate, and correlate these cues to changes in oligodendrocyte lineage specification.
Statement of Benefit to California (as written by the applicant)	We are optimistic that the proposed studies will benefit Californians in two ways. First, by identifying "hubs" of critical transcription factors - the key regulators of cell genetics - in the differentiation pathways of neural stem cells to mature oligodendrocytes, we will enable the use of neural stem cells as a therapeutic treatment for central nervous system diseases. Secondly, we will create a technology that can be applied to understand other similar stem cell differentiation pathways.
Funds Requested	$230,400
GWG Recommendation	***Not recommended for funding***

Total Scoring Data

Final Total Score: 76

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

Mean	78
Median	76
Standard Deviation	4
Highest	85
Lowest	75
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	1
Tier 2 (1-84): Not recommended for funding	13

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	6	2	6
Is the rationale sound?	2	3	9
Is the proposal well planned and designed?	1	5	8
Is the proposal feasible?	1	3	10

Reviewer Comments

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

Strengths

- A very interesting and novel proposal to understand transcription factor activity and fate of neuronal stem cells.

Concerns

- While the science is interesting the potential clinical value of this project is unclear.
- As this is such a well-explored area, it was not clear how much innovation is present in this approach.
- Most of the relevant transcription factors the PI is trying to identify have already been identified. It is therefore not clear how the identification of more transcription factors will be useful given that the distinction between causal and consequential transcription factors have not been addressed.

DISCOVERY

Application #	DISC1-09895
Title (as written by the applicant)	Artificial Intelligence Approach to Directed Differentiation of Human Pluripotent Stem Cells
Research Objective (as written by the applicant)	An artificial-intelligence (AI) system will make connections between networks of genes and proteins involved in developmental stem cell biology and activity fingerprints of small molecules.
Impact (as written by the applicant)	The identification of bioactive molecules will elevate the scalability of GMP manufacturing of differentiated cells for cellular therapies, specifically for RPE transplantation to treat vision loss.
Major Proposed Activities (as written by the applicant)	• Use artificial-intelligence and machine learning to refine the selection of de novo, novel candidate compounds that will differentiate pluripotent human stem cells into retinal pigmented epithelium. • Use iterative screens of novel compounds in cellular assays to generate data that will be compiled into activity matrices specific to each compound. An activity matrix allows AI to analyze the data. • Organize and cluster all of the activity matrices generated from an entire chemical library by using the neural network tool of self-organizing maps (SOMs). SOMs allows AI to identify data trends. • Cross-reference SOMs of small molecule activities, target predictions, and chemical space/structure/pharmacaphores to predict completely novel structures with enhanced differentiation activity. • Apply the novel compounds discovered by artificial-intelligence to direct the xeno-free differentiation of human pluripotent stem cells into RPE. • Characterize the cells generated after exposure to small molecules under xeno-free conditions to confirm acquisition of RPE identity and function.
Statement of Benefit to California (as written by the applicant)	Age-related macular degeneration (AMD) is a leading cause of blindness, and we lack effective therapies. One promising approach is cellular therapy using retinal pigment epithelium (RPE) cells derived from pluripotent stem cells, and several clinical trials have been initiated. However, converting stem cells to RPE can be a lengthy, expensive process. We propose to streamline the production of RPE by using novel artificial intelligence to identify small molecules to speed up the process.
Funds Requested	$150,000
GWG Recommendation	***Not recommended for funding***

Total Scoring Data

Final Total Score: 70

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

Mean	70
Median	70
Standard Deviation	5
Highest	75
Lowest	60
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (1-84): Not recommended for funding	14

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	3	7	4
Is the rationale sound?	1	6	7
Is the proposal well planned and designed?	0	8	6
Is the proposal feasible?	0	7	7

Reviewer Comments

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

Strengths

- This is an exceptionally innovative approach to employ machine learning to generate RPE cells from hPSCs using small molecules.
- This approach has the potential to serve as a template to streamline and improve manufacturing of other cell types from stem cells.
- Potential for impact is high. RPE cells have strong clinical potential but improved clinical manufacturing processes are needed. Small molecules reduce the cost, improve robustness, and reduce animal components in the platform.
- The high level approach is very compelling. Experimental and computational tools are in place. Workflow is clearly designed to implement this project in a timely, efficient manner.
- The team is strong, leveraging expertise and resources in stem cell differentiation and expertise in computational drug development.
- The developmentally-guided stepwise screening approach is a strength.
- This project is not a revolutionary advance but, if successful, it might pave the way for other similar advances in other differentiation protocols.
- Feasibility is a concern but significant progress in Aim 1 could justify this project.

Concerns

- The most innovative part of this proposal, the use of the AI based screen, is not very well described.
- It is not clear how much better the machine learning approach is compared to other approaches for choosing small molecules.
- Details on compound libraries and machine learning algorithms are lacking.
- The specific aims are linear. Aim 2 relies on the success of Aim 1. Aim 3 relies on the success of Aim 2. The concern is that no good candidates will emerge from Aim 1, and therefore Aims 2 and Aims 3 will be unnecessary.

- Starting with a seed library of small molecules, the library is improved through iteration of assay-driven active learning. However, the initial library selection is not adequately described in the proposal.
- This is a high-risk, low-to-moderate reward proposal, and as such is not competitive.
- The proposal may be strengthened by providing at least one of the following: more convincing theoretical or simulation predictions of the probability of success for the computational approaches, examples of previous successes and failures of these approaches, or preliminary data.
- The proposal is to screen using AI to identify small molecules for enhanced differentiation. It is not clear what is the baseline for the respective state-of-the-art conditions and how informative the AI approach is toward identifying new small molecule candidates.
- The timeline seems very ambitious given the scale of the screen, the number of lines and experiments and the fact that scaling the culture of the cells is not trivial.

DISCOVERY

Application #	DISC1-09912
Title (as written by the applicant)	A Novel Tissue Engineering Technique to Repair Degenerated Retina
Research Objective (as written by the applicant)	Transplantation of human embryonic stem cell (hESC) derived retina organoids (hESC-RO) together with hESC derived retinal pigment epithelium (hESC-RPE) to treat advanced retinal degeneration diseases
Impact (as written by the applicant)	Based on the 'proof of concept' experiments in animal models, this novel approach can be translated into a therapeutic product for the treatment of advanced human retinal degenerative diseases.
Major Proposed Activities (as written by the applicant)	• Prepare hESC-RPE implants by culturing hESC-derived RPE cells (from H9 cells) on ultrathin parylene. hESC-RO's will be derived from H9 cells (primarily based on the protocol of Zhong et al., 2014) • A composite graft will be made of hESC-RPE and hESC-RO. A suitable surgical approach will be developed for subretinal placement of the co-graft in rats • Assessment of visual function in transplanted rats by visual behavioral (optokinetic testing) and luminance threshold mapping of the superior colliculus (electrophysiological recording) • Conduct morphological assessments of the tissue samples based on immunostaining and confocal microscopic imaging
Statement of Benefit to California (as written by the applicant)	The proposed co-graft approach will lead to the discovery of a new treatment strategy for retinal degeneration diseases such as age-related macular degeneration (AMD) and retinitis pigmentosa (RP). This approach will be beneficial for late stage disease conditions that are considered to be incurable because it requires replacement of both RPE and photoreceptors. By demonstrating the 'proof of concept' in animal disease models, it is easy to translate our findings to human clinical trials.
Funds Requested	$215,133
GWG Recommendation	***Exceptional merit and warrants funding, if funds are available***

Total Scoring Data

Final Total Score: 85

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

Mean	86
Median	85
Standard Deviation	2
Highest	90
Lowest	85
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	14

Tier 2 (1-84): Not recommended for funding	0

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

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

- Cell therapy for macular degeneration or retinal degeneration must eventually address photoreceptor loss and this proposal addresses this critical issue.
- Replacement of both RPE and photoreceptors will ultimately be required for many conditions.
- There is good preliminary data for applicant's strategy of grafting RPE as an intact cell layer.
- Preliminary data indicating integration of retinal organoid into host circuitry are encouraging.
- The concept that histotypic combination of RPE with retinal organoid will promote proper structural organization of grafts *in vivo* has merit.
- The investigator and the environment are strengths of the proposal.
- The RPE monolayer is currently in clinical trials so this approach is highly translational.
- Improved optokinetic testing is a strength.

Concerns

- No alternative approach is proposed if RPE layer does not prevent rosette formation of retinal organoid.
- Aim 2 is dependent on successful completion of Aim 1.
- The experiments proposed in immunodeficient animals won’t be able to predict implant engraftment and function.
- The approach for making sheets of 3D organoids and how such an approach can be scaled-up for human use are not clear.
- The culture conditions to produce ROs still need to be optimized.
- It is not obvious why the two tissue grafts would attach to each other after transplantation based on hydrophilicity.

DISCOVERY

Application #	DISC1-09922
Title (as written by the applicant)	Development of treatments to improve healing of ischemic wounds
Research Objective (as written by the applicant)	Use a pro-angiogenic proteoglycan mimetic to protect the wound matrix from rapid degradation, and seed with EPCs promote angiogenesis to accelerate ischemic wound healing.
Impact (as written by the applicant)	We expect that a proteoglycan mimetic, combined with a collagen scaffold and EPCs will lead to accelerated healing of ischemic foot ulcers, and reduce limb amputation and mortality rates of patients.
Major Proposed Activities (as written by the applicant)	• Synthesize and characterize the angiogenic potential of mimetic in a collagen scaffold with endothelial progenitor cells • Quantify the effect of a proteoglycan mimetic and EPCs delivered with a 3D collagen scaffold on ischemic wound repair in an in vivo diabetic ischemic wound model
Statement of Benefit to California (as written by the applicant)	We expect that LXW7-DS-SILY combined with a collagen scaffold and EPCs will lead to a novel treatment to accelerate healing of ischemic diabetic foot ulcers, thereby reducing limb amputation and mortality rates of diabetic patients. We further anticipate that the results from the proposed studies will support translational activities to bring this therapy to patients. Ultimately, successful development will have a positive economic and health impact in California.
Funds Requested	$235,800
GWG Recommendation	***Not recommended for funding***

Total Scoring Data

Final Total Score: 80

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

Mean	79
Median	80
Standard Deviation	3
Highest	85
Lowest	75
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	2
Tier 2 (1-84): Not recommended for funding	12

Score Influences

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

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

Reviewer Comments

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

Strengths

- Use of LXW7-DS-SILY conjugate to limit MMP activity and to promote new vessel growth is an interesting approach with both merit and potential feasibility.
- Overall, the combined the approach of promoting angiogenesis while protecting matrix degradation and preventing diffusion of proangiogenic factors away from the wound has merit.
- The approach for stabilizing collagen fibers and preventing scar formation by proteoglycan biomimetics has merit.
- The approach of delivering LXW7 peptide tethered to a scaffold provides critical advantages over delivery of VEGF.
- The project has a clear translational focus on developing cell and scaffold treatments for diabetic foot ulcers
- The use of a VEGFR2 activating peptide to mobilize endothelial progenitor cells (EPCs) for angiogenesis is logical and innovative in the context of the PI's decorin-mimetic scaffold.
- There is excellent justification for addressing challenges associated with chronic wounds.
- This is a strong, interdisciplinary research team with translational experience in developing regenerative therapies.
- The *in vivo* model is appropriate for the translational goals of the study. The modified wound model replicates diabetic foot ulcers in a more physiologically relevant manner. The study of control and treatment in the same mouse is also a strength of the study design.
- The PI provided a detailed description of conjugation strategies and validation of obtained product.

Concerns

- The cellular aspect of the construct is underdeveloped. The lack of detail regarding the EPC source is a concern.
- It is not clear that EPCs will be necessary for efficacy. Recruitment of native EPCs is not considered and control scaffolds without cells are lacking.
- The proposed *in vitro* angiogenesis assays in Aim 1 are not representative of angiogenesis *in vivo*. Thus the use of these assays to identify a single formulation might be too restrictive.
- The rationale for transplantation of endothelial progenitor cells has been explained by the PI (traffic of EPCs won't target the avascular wound) but it is still questionable given the need for chronic immunosuppression to prevent cell rejection and the potential negative influence of immunosuppressive drugs on revascularization and wound closure.
- Data is not adequately provided to demonstrate that tethered LXW7 is as functional as untethered peptide and that the differently modified SILY is still functional.
- The poor resolution of Figure 1 makes it difficult to interpret the data.

DISCOVERY

Application #	DISC1-09923
Title (as written by the applicant)	Exploring mechanisms controlling proximal-distal progenitor cell fate in the human lung
Research Objective (as written by the applicant)	Our goal is to determine the origin and fate of a newly identified progenitor cell population in human fetal lung and the signals required for its restriction to a distal fate.
Impact (as written by the applicant)	The data generated will be essential for optimizing cell lineage based therapy for diseases of the lung gas exchange surface.
Major Proposed Activities (as written by the applicant)	• To determine the origin and fate of the human specific lung progenitor cell population in our a 3D explant culture model that closely mimics in vivo lung development in humans. • To define the signaling pathways necessary for the maintenance versus differentiation of SOX2+/SOX9+ versus SOX2-SOX9+ distal progenitor cell identities in our 3D human lung organ culture model.
Statement of Benefit to California (as written by the applicant)	37 counties in California with a total population of 38.8 millions have higher levels of chronic lung disease than all the US with a life expectancy of 32 years in California vs 42 nationwide. This proposal will deliver critical information about the human specific signaling pathways supporting epithelial distal fate determination, thus identifying specific molecules that could be used to re-program iPSC into distal alveolar lineages to be used in stem cell therapies for the people of California
Funds Requested	$210,627
GWG Recommendation	***Not recommended for funding***

Total Scoring Data

Final Total Score: 65

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

Mean	65
Median	65
Standard Deviation	6
Highest	70
Lowest	50
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (1-84): Not recommended for funding	14

Score Influences

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

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

Reviewer Comments

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

Strengths

- The hypothesized origin of Sox2+Sox9+ cells from a Sox2+ progenitor is logical although not particularly innovative.
- The lung explant culture is innovative and a strength of the proposal. This model will allow a more detailed investigation of stem cells in the lung.

Concerns

- The investigators have excellent experience in lung development but the project would benefit from expertise in translational lung regenerative therapies.
- The impact of this mechanistic research project on eventual development of translational therapies is not clear.
- The proposal has a very limited hypothesis and unclear translational impact.
- Aim 1 lacks molecular or functional characterization of the Sox2+Sox9+ progenitor population.
- The plan to track Sox2/Cited1 labelled cells to test the hypothesis in Aim 1 is unclear.
- The relationship between mesenchymal cells and developmental signaling pathways in Aim 2 is not clearly described. It isn't evident how signals will be traced to mesenchymal cells.
- RNAseq is not sufficient to establish intercellular signaling mechanisms in Aim 2.
- There is not sufficient investigation of the regenerative potential of the cell populations studied.

DISCOVERY

Application #	DISC1-09931
Title (as written by the applicant)	Validation of a human induced pluripotent stem cell derived neuromuscular co-culture platform for disease modeling and drug discovery
Research Objective (as written by the applicant)	To further optimize a co-culture platform of hiPSC-derived skeletal myotubes and spinal motor neurons for assays related to neuromuscular disease.
Impact (as written by the applicant)	Development of this co-culture platform will provide novel methodology to interrogate neuromuscular disease phenotypes and aid in screening therapies.
Major Proposed Activities (as written by the applicant)	• To further characterize morphology and function of human iPSC-derived NMJs in a co-culture system. • To characterize the electrophysiological profile of iPSC-derived NMJ-related transmission. • To characterize the evoked calcium response in sKM following optogenetic stimulation of MNs in ALS.
Statement of Benefit to California (as written by the applicant)	Neuromuscular and neurodegenerative disorders affect millions of patients and family members in California. In order to decrease the burden on patients and affected families as well as decrease healthcare costs for other citizens, we must develop innovative strategies to provide new insight into disease mechanisms for therapy. This proposal provides a platform that can be adapted by both academic and industry researchers to accomplish these goals.
Funds Requested	$204,187
GWG Recommendation	***Not recommended for funding***

Total Scoring Data

Final Total Score: 70

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

Mean	70
Median	70
Standard Deviation	1
Highest	73
Lowest	70
Count	13
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (1-84): Not recommended for funding	13

Score Influences

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

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

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

- Most studies focusing on the NMJ to date do not use myotubes and motor neurons derived from the same patient iPS cell line. In this respect, the proposal is innovative.
- Establishment of an *in vitro* system to study the NMJ may create opportunities for drug discovery.
- Rationale for the proposal is sound and experiments are overall well planned.
- *In vitro* NMJs could be an excellent system to screen therapeutic drugs.

Concerns

- It is not clear how the end-product will be used to investigate ALS. For example, what type of readout will be assayed, once the *in vitro* cell system is developed? Will the system support high-throughput screening of drug candidates?
- There is not a strong link between neuromuscular disease and the proposed experiments.
- The concept may be new with regard to using patient-derived cells but studies on modeling the NMJ *in vitro* have been done since the 1980s.
- For this project to be feasible the first requirement is to have efficient generation of both cell types: myotubes and motor neurons. The provided data raises concern about the purity and efficiency of generated myotubes. For example, myogenin is a marker of differentiation and should not coincide with Pax7 expression.
- No evidence is provided of an ability to detect disease relevant outcomes.
- As disease has later onset, the value of studying the early processes in these investigations is not clear.
- It is commented in the experimental plan that healthy NMJs may degrade after 7 days and that optogenetics may help extend culture. This raises concerns about feasibility since the point is to have a model to study at least relatively long-term timepoints.
- The last aim of the proposal only investigates the difference between patient-derived and isogenic iPS cell function. This does not address how the system being developed will, in the future, address disease.

DISCOVERY

Application #	DISC1-09949
Title (as written by the applicant)	Human pluripotent stem cell-derived satellite-like cells for skeletal muscle regeneration
Research Objective (as written by the applicant)	We aim to test a human pluripotent stem cell-derived cell population to achieve long-term muscle engraftment in vivo to ultimately develop a cell therapy to treat muscle damage due to various causes.
Impact (as written by the applicant)	The project is the first step towards a cell therapy that overcomes current imitations for muscle directed therapy and could provide treatment options for a range of diseases with large unmet needs.
Major Proposed Activities (as written by the applicant)	• We propose to test intermediate cell populations generated by our well-established and published differentiation protocol and test their engraftment capacity in a mouse hindlimb injury model. • The most efficacious cell population from Activity 1 will be further sorted into subpopulations and their engraftment capacity and ability to populate the satellite cell niche will be determined. • The sorted cell subpopulations from Activity 2 will be characterized in vitro via a range of cell biology and genomic methods.
Statement of Benefit to California (as written by the applicant)	The incapacitating and chronic loss of muscle during normal aging (sarcopenia), cancer (cachexia) and/or various muscular dystrophies, is a problem that affects many people's life-span, quality of life and add undue burden to societal cost. In all these diseases or conditions treatment conditions are limited and not curative. The work in this proposal brings a potentially curative muscle stem cell therapeutic closer to translation into clinical studies.
Funds Requested	$148,500
GWG Recommendation	***Not recommended for funding***

Total Scoring Data

Final Total Score: 75

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

Mean	72
Median	75
Standard Deviation	10
Highest	80
Lowest	45
Count	13
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (1-84): Not recommended for funding	13

Score Influences

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

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	3	8	2
Is the rationale sound?	2	7	4
Is the proposal well planned and designed?	0	7	6
Is the proposal feasible?	1	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

- *None noted*

Concerns

- The proposal lacks novelty (low risk, low reward). Several transgene-free protocols, claiming to generate satellite cells *in vitro,* have been published in the last couple of years.
- The proposed project will not identify culture conditions for using hPSCs to generate satellite cells. The experiments will only identify at what stage the current culture conditions contain a population of satellite cells.
- No convincing evidence is provided that *in vitro* generated myogenic cell preparations have *in vivo* regenerative potential.
- Insufficient attention is paid to meaningful changes in a published protocol that generates muscle fibers with little evidence of a satellite cell or stable progenitor stage.
- If transplantation of cells from various stages fails, Aims 2 and 3 cannot be completed.
- It is not clear what stages will be looked at in the *in vivo* model. The proposal states that 3-4 stages will be examined but it is unclear if these are the stages when the cells express Pax/7/CD56 *in vivo*.
- There is concern whether the PI will be able to obtain large enough quantities of cells for the correct type for injection.
- It is not clear how the team will enrich for satellite cells.

DISCOVERY

Application #	DISC1-09956
Title (as written by the applicant)	Opposing roles of Cerberus1 and Gremlin1 in hESC exit from pluripotency
Research Objective (as written by the applicant)	We hypothesize that the secreted DAN family proteins CER1 and GREM1 control hESC pluripotency and modulate the transition to definitive endoderm.
Impact (as written by the applicant)	Understanding the role CER1 and GREM1 play in differentiation will accelerate the generation of purified populations of differentiated hESCs, suitable for therapeutic use, without teratoma formation.
Major Proposed Activities (as written by the applicant)	• Specific Aim 1: Characterize the role of CER1 and GREM1 in maintenance of pluripotency and directed differentiation to DE in multiple hESC lines. • Aim 1a. Use CRISPR to generate hESC cell lines to study the effects of CER1 and GREM1 on hESC pluripotency and DE formation. • Aim 1b. Biochemical characterization of CER1 and GREM1 on hESC function. • Aim 1c. Monitor DE formation in real time live in wild type, CER1 and GREM1 CRISPR cell lines. • Specific Aim 2: Determine whether CER1 and GREM1 can directly signal in hESCs.
Statement of Benefit to California (as written by the applicant)	Impact of proposed studies. Validation of CER1 and GREM1 as regulators of hESC pluripotency and definitive endoderm (DE) formation will provide new insight into how cells communicate with the extracellular environment and provide answers to the questions about why individual hESC lines form teratomas and have different differentiation potentials. Together, the findings will accelerate the rate at which hESCs can be applied to treat human disease.
Funds Requested	$232,200
GWG Recommendation	***Not recommended for funding***

Total Scoring Data

Final Total Score: 70

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

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

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

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

- DAN and CER1 are important regulators of signaling pathways but their role in pluripotency is poorly understood.

Concerns

- This is a very interesting basic human pluripotent stem cell biology project but the main reasons given for significance, namely differentiation bias and teratoma risk, are not very convincing.
- This is not a high impact proposal.
- Overall proposal is very narrow with limited innovation.
- The research plan does not examine the alternative and more likely hypothesis that these factors in fact bind known regulators, as they are known to do in many other systems.
- Evidence that DAN and CER1 might act directly on signal transduction pathways is not compelling.
- It is unclear how the findings will impact directly on the issue of teratoma formation or cell line differentiation bias.
- The investigator's claim that endoderm cells form teratomas more readily is not supported by the bulk of the literature.
- The approach in Aim 1 is reasonable but could have been described more thoroughly.
- Aim 2 will provide very limited insights.

DISCOVERY

Application #	DISC1-09957
Title (as written by the applicant)	Development of a Pleiotrophin Monoclonal Antibody to Reduce Leukemic Stem Cell Growth
Research Objective (as written by the applicant)	The objective of this study is block leukemic stem cell growth using an antibody based therapy.
Impact (as written by the applicant)	This research may lead to a curative therapy for patients with stem cell derived leukemias, such as chronic myeloid leukemia.
Major Proposed Activities (as written by the applicant)	• To develop a panel of antibodies which target a signaling pathway that enables leukemic stem cell survival. • To validate the antibodies block activation of the target signaling pathway. • To validate the antibodies reduce leukemic stem cell growth in vitro.
Statement of Benefit to California (as written by the applicant)	Leukemias such as chronic myeloid leukemia (CML) are prevalent among the general American population. While treatment for CML has advanced significantly with the advent of tyrosine kinase inhibitors such as gleevec, there is still no curative treatment because leukemia stem cells are refractory to these treatments. In this application, we propose to directly target and eliminate leukemic stem cells with an antibody based therapy that could potentially cure CML and other leukemias.
Funds Requested	$230,400
GWG Recommendation	***Not recommended for funding***

Total Scoring Data

Final Total Score: 80

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

Mean	78
Median	80
Standard Deviation	5
Highest	80
Lowest	65
Count	13
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (1-84): Not recommended for funding	13

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	5	2	6
Is the rationale sound?	2	1	10

Is the proposal well planned and designed?	1	3	9
Is the proposal feasible?	2	1	10

Reviewer Comments

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

Strengths

- The main strengths of the proposal are the previous work showing the role of PTN in cancer stem cell maintenance and growth and the likelihood that mAb interference will have an impact.
- An important strength of the proposal is the preliminary data using mice deficient for PTN as host for CML transfer assays.
- There is intrinsic risk involved in mAb discovery work, but this issue is lessened by the availability of some anti-PTN mAb that appear to block the pathway, and by the collaborators who have been brought on to be part of team.
- The resources at the applicant institution are excellent.

Concerns

- The proposed studies are feasible but do not address the role of PTN in human CML LSCs.
- In some patients CML appears to be cured following a prolonged period of TKI administration. Prolonged TKI use has recently been reported to have little long-term toxicity. Thus, CML may not represent a major medical need compared to many other diseases in which few effective therapies exist.
- The preliminary data are conflicting as the factor previously identified in regulating normal hematopoiesis is now found to have no impact. The safety of this approach is questionable.
- Evidence that CML LSCs are dependent on MAPK signaling is lacking, and it is unclear if this would be the case as these cells are largely quiescent.
- The majority of the data are from a murine model of CML. The human data are not indicative of LSC biology as CD34+ cells are largely progenitors.
- The independence of the PI is not clear.

DISCOVERY

Application #	DISC1-09960
Title (as written by the applicant)	Reversion of Cellular Hallmarks of Aging through Transient Somatic Reprogramming
Research Objective (as written by the applicant)	We aim to develop a rejuvenation protocol based on transient induced pluripotent stem cell (IPSC) reprogramming scalable to entire tissues and organs, for systemic and sustainable rejuvenation.
Impact (as written by the applicant)	The ultimate goal of our research is to establish the basis for treatments to restore aged patients to the youthful state. Beyond just extending lifespan, this therapy would restore quality of life.
Major Proposed Activities (as written by the applicant)	• Transcriptome profiling in single cells before and after transient reprogramming. • Test whether reprogramming-induced cellular rejuvenation can be achieved by treatment with small molecules. • Test the effect of transient reprogramming on age reversion in vitro cultured satellite cells. • Test the effect of transient reprogramming on age reversion in ex vivo cultured muscle fibers. • In vivo delivery of reprogramming mRNAs to different tissues and organs. • Assessment of rejuvenation at the cellular and systemic level.
Statement of Benefit to California (as written by the applicant)	The number of Americans over 65 is expected to double from 46.2 M in 2014 to 98 M in 2060, rising from 15% to >20% of the total population. In concordance, recent estimates predict that delaying aging by just 2 years would save $7.1 trillion in health care costs over 50 years. If successful this line of research will have fundamental impact in the field of aging.
Funds Requested	$230,453
GWG Recommendation	***Not recommended for funding***

Total Scoring Data

Final Total Score: 65

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

Mean	67
Median	65
Standard Deviation	9
Highest	85
Lowest	50
Count	13
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	1
Tier 2 (1-84): Not recommended for funding	12

Score Influences

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

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

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

- The proposal presents a novel approach to reversal of aging based on compelling preliminary data.
- Most rejuvenation studies are flawed. More deep knowledge of the aging process and specific targeting are required.
- The proposed studies will yield important findings even if translation is some way off.
- The plan to address satellite cell aging is good and supported by a strong collaboration.
- The small molecule approach will provide a more realistic route to therapy.

Concerns

- The scientific rationale that transient reprogramming of somatic cells with reprogramming factors will promote "rejuvenation" and counteract aging is not strong.
- This proposal is high risk but not high reward.
- Descriptive preliminary results on gene expression changes do not imply that these will result in an improved functional outcome.
- The experimental plan is largely descriptive.
- Studies of the ability of rejuvenated muscle stem cells to achieve functional regeneration (and generate functioning fibers *in vivo*) is critical but may be beyond scope of the study.
- The perdurance of the rejuvenation effect is key to future application of this strategy. There is a fine line between reversal/rejuvenation and the "point of no return."
- The proposal is extremely ambitious and likely will not be possible to accomplish in 12 months. Just one aim may take the entire proposed 12-month funding period.
- Genes will be identified that are markers of the “rejuvenated signature”, but there is no discussion of how these markers will be tested or validated.
- The identification of small molecules that can induce “rejuvenation” is poorly described.
- The overall goal is to rejuvenate cells. It is not clear how the team will stop the cells from completing differentiation.
- The application provides data that cells were reprogrammed using standard techniques, and then “relaxed” the cells for a few days (up to 6). Very little data is shown to demonstrate that these cells were not “transformed”. While Aim 1, single cell sequencing, will investigate the fate of cells after reprogramming, the proposal that these cells maintain their “rejuvenated” state is unsupported.
- The “rejuvenation” of cells appears to wane after 6 days. The PI proposes repeated transformation of cells. It is doubtful that almost continued treatment of cells by small molecules and/or transformation factors will be a viable treatment option.

DISCOVERY

Application #	DISC1-09970
Title (as written by the applicant)	Prevention of the metastasis through cancer stem cell-specific targeting using nanomedicine
Research Objective (as written by the applicant)	Our objective is to prevent the metastasis by developing specific targeting against cancer stem cells (CSC) using highly versatile nanoporphyrin as well as high affinitive ligand of biomarker of CSC.
Impact (as written by the applicant)	Successful execution of this proposed project will serve as an excellent attempt for developing novel targeted therapy for eliminating disseminated CSC to prevent the metastasis of malignant diseases.
Major Proposed Activities (as written by the applicant)	• Synthesize peptidomimetic ligand (LLP2A)-targeted and doxorubicin-loaded nanoporphyrin. • Investigate the cellular uptake and cytotoxicity of these nanoporphyrin in cancer stem cells. • Establish animal model with metastasis by subcutaneous injection of cancer stem cells into NSG mice. • Administer nanoparticles containing doxorubicin after the transplantation of cancer stem cells. • Optical imaging for monitoring the metastasis development after the injection of cancer stem cells and administration of nanoparticles. • Evaluate the extent of metastasis prevention at the end point.
Statement of Benefit to California (as written by the applicant)	Over 90% of cancer death is associated with relapse and metastasis which are caused by cancer stem cells (CSC), development of specific-CSC targeting is an excellent attempt for developing novel targeted therapy for eliminating CSC to prevent the metastasis of malignant diseases, the outcome will ultimately improve survival and quality of life of California's patients with cancers, and boost California's biotechnological and pharmaceutical industry on therapeutics address to unmet medical needs.
Funds Requested	$235,800
GWG Recommendation	***Not recommended for funding***

Total Scoring Data

Final Total Score: 79

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

Mean	77
Median	79
Standard Deviation	4
Highest	80
Lowest	70
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0

Tier 2 (1-84): Not recommended for funding	14

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	2	5	7
Is the rationale sound?	0	5	9
Is the proposal well planned and designed?	0	6	8
Is the proposal feasible?	1	5	8

Reviewer Comments

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

Strengths

- Hepatocellular carcinoma is a deadly disease with few treatment options.
- The combined theranostic approach of the nanoparticles (drug delivery and imaging) is a strength of the proposal.
- The nanoparticle platform is novel.
- The investigators are experienced in liver biology.
- The necessary resources are present at the institution.
- The aims are feasible and clearly presented.

Concerns

- It is not clear that HCC CSCs are being targeted in the application.
- The experiments rely upon a single cell line. In addition, no clinical specimens will be studied.
- Most of the effort will go into models that may not translate directly to a disease application.
- The specificity of the nanoparticles is unclear.
- It is not clear whether the synthesis of the nanoparticles can be scaled up for clinical use.
- There is concern about the potential for non-specific targeting of blood circulating MSCs.
- It is unclear if the nanoparticles are internalized after binding.
- Figure 5 is missing the control MSCs.

DISCOVERY

Application #	DISC1-09973
Title (as written by the applicant)	Human Pancreatic Beta-Cell Regeneration by Islet Cell Transdifferentation
Research Objective (as written by the applicant)	The scientific objective is to extend a newly developed system to induce islet cell transdifferentiation to test in vivo with human islet cells our model of islet cell transdifferentiation.
Impact (as written by the applicant)	Success in developing a purely pharmacological approach to treat diabetes by regenerating beta-cells from endogenous stem/progenitors would have an enormous impact on this disease.
Major Proposed Activities (as written by the applicant)	• SPECIFIC AIMS. The goal of this aim is to test in vivo with human islet cells our model of islet cell transdifferentiation. • Aim 1. Induction of transdifferentiation in intact islets in vitro followed by transplantation in vivo. • Aim 2. Induction of human islet cell transdifferentiation in vivo without prior beta-cell ablation.
Statement of Benefit to California (as written by the applicant)	Diabetes is a major public health problem in California. According to the Diabetes Coalition of California, 3 million Californians have diabetes and about 1 in 3 have prediabetes. While most of those cases are type 2 diabetes, the prevalence of type 1 diabetes has also been increasing. Thus, our therapy, which would be much less expensive than a transplantation approach and is potentially applicable to both type 1 and type 2 diabetes, could have a major effect on the health of Californians.
Funds Requested	$265,500
GWG Recommendation	***Not recommended for funding***

Total Scoring Data

Final Total Score: 70

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

Mean	70
Median	70
Standard Deviation	0
Highest	70
Lowest	70
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (1-84): Not recommended for funding	14

Score Influences

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

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

- This proposal will address an unmet need by developing beta cell replacement therapy for patients with diabetes.
- The novelty of this proposal is to study regulation and protocols that may allow human alpha to beta cell transdifferentiation using pharmacological approaches by transplanting into a mouse model.
- The relative novelty of the approach for increasing beta cell mass in type 1 and type 2 diabetes is a strength.
- The possibility that beta cells transdifferentiated from alpha cells may be more resistant to autoimmunity triggers (like viral infection and resulting immunogenicity) than native beta cells and therefore more resistant to autoimmune destruction in type-1 diabetes is a strength.
- The proposal has a strategy for distinguishing neogenic from preexisting beta cells.
- An important therapeutic aspect of this proposal is that success could lead to the development of a protocol that can be applied in patients with type 2 diabetes who retain a substantial number of beta cells.

Concerns

- The use of a mouse model, while justified for early work, will be unlikely to aid in rapid translation.
- Insufficient details are provided with regard to experimental design and expected outcomes.
- Results of the proposed studies may not allow for conclusive interpretation whether, and to what degree, alpha to beta cell transdifferentiation occurred.
- In vivo experiments are in the mouse model. The mouse studies are unlikely will be sufficient for translation to clinic.
- No stem cells will be used in the application and there is no clear evidence of alpha to beta switch.
- The proposed argument that alpha to beta switched cells are less immunogenic is flawed.
- The statement that beta cells are not present in patients with type-1 diabetes is incorrect since evidence from the research on nPOD samples has shown residual beta cells in many type-1 diabetic pancreases.
- The statement that therapeutic interventions to block autoimmunity are available is incorrect. There is no therapy for re-establishing tolerance toward beta cells.
- From a therapeutic point of view it is not clear for how long insulin blockade needs to be performed in the patients and whether exogenous insulin supplementation may be withdrawn with all the associated risks.
- No functional characterization of transdifferentiated beta cells is proposed. It is known that perfusion glucose-stimulated insulin secretion (perfusion assay) is necessary to truly assess beta cell maturity.
- It is not clear how the RNA will be isolated selectively from transplanted cells and not from host tissue.
- Intrapancreatic cell transplants have a high risk of inducing pancreatitits thereby introducing site-dependent variability due to presence of higher amounts of trypsin in the intrapancreatic site.

DISCOVERY

Application #	DISC1-09976
Title (as written by the applicant)	Anti-inflammatory mesenchymal stem cells 2 (MSC2) as a disease-modifying therapy for Huntington's disease
Research Objective (as written by the applicant)	The overall goal of our study is to demonstrate efficacy of a new anti-inflammatory mesenchymal stem cell-based product, "MSC2" cells, in established mouse models of Huntington's disease.
Impact (as written by the applicant)	The demonstration of efficacy of our novel MSC2 treatment in HD mouse models will advance a novel MSC-based product, "MSC2", for the safe and effective treatment of Huntington's disease in patients.
Major Proposed Activities (as written by the applicant)	• We will determine the safety and efficacy of anti-inflammatory MSC2 treatment over conventional MSC treatment in two different mouse models of Huntington's disease. • We will identify potential mechanisms of action associated with MSC2 efficacy by measuring levels of inflammatory markers in brain and blood of treated HD mice using multiplex immunoarrays.
Statement of Benefit to California (as written by the applicant)	Approximately one in 10,000 CA residents has HD, which has no effective treatment or cure and results in enormous financial and emotional costs for friends, families and caregivers. California has a particularly strong HD community, including researchers, physicians, patient advocates and caregivers all working together towards finding a treatment for this devastating disorder. Our work should lead to the development of a new stem cell-based treatment for Californian HD patients.
Funds Requested	$301,266
GWG Recommendation	***Not recommended for funding***

Total Scoring Data

Final Total Score: 75

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

Mean	74
Median	75
Standard Deviation	8
Highest	90
Lowest	60
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	2
Tier 2 (1-84): Not recommended for funding	12

Score Influences

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

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

Reviewer Comments

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

Strengths

- The goal of the proposal is to decrease inflammation, which may contribute to Huntington's disease (HD).
- The MSC2 cells have been shown previously to have decreased inflammatory markers.
- *In vitro* studies, using an HD model, suggest that MSC2 cells can improve metabolic activity.
- Preliminary analysis of an HD mouse model also suggested that MSC2 cells can improve motor function. However, the mouse model only looked at MSC2 vs PBS effects (MSC or MSC1 cells were not examined making it difficult to conclude that the effect was MSC2-specific).
- Aim 1 will examine the effect of i.p. injection of MSC2 cells in two mouse models of HD. Extensive behavioral assays will be used to determine if the injections improve function.

Concerns

- This is an important but narrowly focused proposal for HD, as neither the role of inflammation or the influence mesenchymal cells have been proven to be causal rather than consequential to the disease.
- It is not clear if the proposed route of administration will produce an effect on the brain. The PI states that MSC2 cells likely will not cross the blood-brain barrier. However, they do expect an effect in the brain due to peripheral/brain cell communication.
- It is not known if there will be an effect on the brain based on the proposed experiments. However, improvement only outside the brain in HD patients could be a major improvement in HD treatment.

DISCOVERY

Application #	DISC1-09978
Title (as written by the applicant)	Effects of Human Neural Progenitor Cells on Chronic Pain Outcomes after Severe Spinal Cord Injury
Research Objective (as written by the applicant)	We propose to test whether human neural stem cells (NSCs) implanted into the severely lesioned spinal cord will modify post lesion molecular responses to attenuate chronic pain.
Impact (as written by the applicant)	Enhancing our understanding of pain biology after severe SCI. Identifying if strategies that repair severe SCI can also attenuate pain. Results will change the standard of care for SCI patients.
Major Proposed Activities (as written by the applicant)	• Determine the effects of human NPC grafts on pain modalities after severe SCI and test whether these grafts alter sensory function “below level” while inhibiting neuropathic pain “above level”. • Identify changes in molecular and cellular mediators in spinal cord circuits and DRG that underlie pain related behaviors after human NPC grafting in severe SCI.
Statement of Benefit to California (as written by the applicant)	Pain develops in 70% of patients with SCI and is a strong predictor of reduced quality of life. A critical component of the translational path is to identify if neural repair strategies affect pain outcomes. NSC therapies for SCI are on a clinical translational path and the work proposed is an essential component of this translational effort. Californians comprise a large population of individuals suffering from chronic pain due to multiple types of traumatic injuries, including SCI.
Funds Requested	$232,200
GWG Recommendation	***Not recommended for funding***

Total Scoring Data

Final Total Score: --

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

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

Score Influences

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

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

Reviewer Comments

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

Strengths

- The proposal addresses an important issue in cell therapy for spinal cord injury (SCI).
- The preclinical studies are promising.
- The proposed model of SCI may be more clinically relevant.
- Some mechanistic studies aimed at identifying origins of pain post transplant for SCI are proposed.

Concerns

- There is little integration with past work on cells that cause pain.
- There is no rationale as to why this approach would work.
- The connection between stem cells and pain is farfetched and does not fall within the objectives of the RFA.

DISCOVERY

Application #	DISC1-09984
Title (as written by the applicant)	Hypo-immunogenic cardiac patches for myocardial regeneration
Research Objective (as written by the applicant)	To engineer a cardiac patch to restore function after a heart attack while avoiding an immune response ("hypo-immunogeneic" CP) when transplanted into a genetically distinct ("allogenic") individual.
Impact (as written by the applicant)	By making hypo-immunogeneic CPs and functional cardiac cells (induced pluripotent stem, "iPS" cells) available to commercial/research entities, our study can fuel the transformation of healthcare.
Major Proposed Activities (as written by the applicant)	• To generate human cardiac patches using human hypo-immunogeneic iPS cell-derived cardiomyocytes and endothelial cells and perform optical mapping of the epicardial surface after transplantation. • To study the survival of hypo-immunogeneic cardiac patches after myocardial infarction as well as their immunological acceptance and integration.
Statement of Benefit to California (as written by the applicant)	Cardiac patches with hypo-immunogeneic iPS cells have potential to restore function and prevent immune rejection, eliminating costly complications of systemic immunosuppression after pluripotent stem cell transplantation. 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 regeneration therapy, which would generate significant future revenues for the State of California.
Funds Requested	$238,500
GWG Recommendation	***Exceptional merit and warrants funding, if funds are available***

Total Scoring Data

Final Total Score: 85

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

Mean	85
Median	85
Standard Deviation	2
Highest	88
Lowest	80
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	13
Tier 2 (1-84): Not recommended for funding	1

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	12	0	2
Is the rationale sound?	9	0	5
Is the proposal well planned and designed?	10	0	4
Is the proposal feasible?	7	2	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

- Hypoimmunogenic iPSCs would have significant impact by enabling allogeneic therapies, which are more scaleable and cost effective than autologous therapies.
- An off-the-shelf, hypo-immunogenic cardiomyocyte is highly desirable and impactful.
- The project has the potential to have significant impact on many different cell therapies using iPSC-derived cells.
- The general concept and approach are well founded and a major strength of the proposal are the preliminary results establishing feasibility of the proposed work.
- The proposal has many well thought out and state of the art analyses of the grafted tissues, including excellent *in vivo* models.
- The notion that an off-the-shelf set of iPSCs can be generated represents an important goal, the approach makes perfect sense, and the preliminary data with mouse cells supports this approach.
- The investigators have been successful in generating murine hypoimmunogenic iPSCs and are making progress in human iPSCs. The project has strong feasibility and good momentum.
- The PI has made important contributions to the field of iPSC derived tolerance and has assembled a great team of collaborators to perform the proposed work.
- The investigators assembled a strong multidisciplinary team with the expertise to perform the proposed project. All necessary pieces are in place to perform the project in a timely manner.
- Assessing immune response in the mice is a strength, as is the use of humanized mice.

Concerns

- Cardiac patches may not be the best proof of concept for immune rejection. Survival of transplanted patches is very low through time even in immune compromised animals.
- The heterotypic transplant model makes functional analyses difficult to interpret.
- There is a lack of details on patch assembly and characterization.
- NK cells and minor histocompatibility mismatches will ultimately result in the rejection of the cells.
- The main weakness of the proposal comes from a lack of consideration of NK cells and their potential role in rejection. This is due to the fact that NK cells would be activated by the absence of MHC I, via the loss of self recognition pathway. Thus, the PI would be encouraged to also provide another fetal-maternal interaction to the proposed work, which can be in the form of HLA E expression, which would serve the purpose of preventing NK cell activation.

DISCOVERY

Application #	DISC1-09989
Title (as written by the applicant)	Development of epigenome-editing biologics for stem cell fate specification
Research Objective (as written by the applicant)	Develop technology capable of targeted editing of epigenetic signatures. Then exploit epigenetic modulation in human embryonic stem cell differentiation into cardiomyocytes a model system.
Impact (as written by the applicant)	The results will not only be transformative for cardiac applications, but they will be widely applicable to optimizing differentiation and reprogramming strategies for human stem cells.
Major Proposed Activities (as written by the applicant)	• Investigate hypomethylation in cells using targeted DN DNMT1 overexpression • Enhance cardiomyocyte lineage commitment in embryonic stem cells • Enhance induced cardiomyocyte (iCM) reprogramming
Statement of Benefit to California (as written by the applicant)	The strategies for generating more mature, stable cardiomyocyte lineages will be utilized in creating patient specific platforms to understand the progression of heart disease after a myocardial infarction in patient specific engineered cardiac tissues.
Funds Requested	$223,204
GWG Recommendation	***Not recommended for funding***

Total Scoring Data

Final Total Score: 70

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

Mean	71
Median	70
Standard Deviation	6
Highest	84
Lowest	65
Count	13
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (1-84): Not recommended for funding	13

Score Influences

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

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

Is the proposal feasible?	0	5	8

Reviewer Comments

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

Strengths

- The focus on regulation of epigenetics during differentiation and reprogramming is a strength. This is an understudied and underutilized factor in controlling stem cell fate.
- Epigenome editing is largely unexplored. The potential of epigenome editing is vast.
- The approach of editing the epigenome is of current interest to the field.
- The use of dominant negative DNMT1 has advantages over nonspecific small molecule DNA methylase inhibitors.
- The epigenetics and cell line development aspects of the experimental plan are clearly designed.
- Contractile characterization of cardiomyocytes is a strength.

Concerns

- Cardiomyocyte differentiation and reprogramming expertise is notably lacking. Methods used to generate and characterize the cells are not standard in the field.
- It is not clear why the investigators expect dominant negative DNMT1 to have substantially different effects on cardiomyocyte differentiation and reprogramming compared to 5-aza-C.
- The proposed tools for epigenome editing are rather blunt. Dominant negative DNMT1 for methylation inhibition could have far-ranging and non-specific effects.
- Genome wide modification of DNA methylation is unspecific.
- No evidence is provided that DNMT1 dominant negative will work.
- The use of a genetic construct to inhibit DNA methylases has greater translational challenges compared to using small molecule inhibitors.
- Why not focus entirely on CRISP/dCas9 mediated targeted approach?
- The proposed patterning and motility studies are not relevant to the scope of the project.
- The proposed studies to generate heart on a chip is a separate project with little connection to the rest of the proposed work.
- It is not clear that this approach would improve cardiomyocyte maturation, which is the main bottleneck in the field.
- The proposed research is very basic and the results would not sufficiently enable clinical translation.
- Statistical analysis is insufficiently described.

DISCOVERY

Application #	DISC1-09990
Title (as written by the applicant)	Direct in vivo reprogramming of organism native differentiated tissue into precursors of the same lineage as a novel safe regenerative paradigm.
Research Objective (as written by the applicant)	To develop drugs for reprogramming differentiated tissue back to its own stem cells as a new cure for degenerative diseases that is safer, more effective and less costly than iPSC methods.
Impact (as written by the applicant)	This will enable a new effective and safe way to regenerate tissues when stem / progenitor cells become lacking, rejuvenate tissues and broadly enhance the efficiency of technology such as CRIPSR.
Major Proposed Activities (as written by the applicant)	• Test our already identified compounds for de-differentiation and reprogramming of in vivo mouse muscle back to its own stem/progenitor cells. • Test our already identified compounds for de-differentiation and reprogramming of humanized muscle in culture and in vivo in an immunotolerant experimental mouse model. • Establish the effective doses, maximal tolerable dose and toxicity of the novel compounds. Low toxicity is expected based on work in progress. • Characterization of these novel muscle stem/progenitor cells, reprogrammed back from differentiated tissue, to confirm that these are safe and not tumorigenic.
Statement of Benefit to California (as written by the applicant)	Californians will be employed in developing, conducting of these studies and in providing reagents and supplies. The therapeutic outcomes of this work will be beneficial for treatment of muscle wasting (genetic and acquired in old age, low gravity, bed riddance, etc.) and will lead to the broader cures for degenerative diseases of other than muscle tissues (heart, brain, liver, etc.), leading to the recovery from illness and improving quality of life of Californians.
Funds Requested	$235,800
GWG Recommendation	***Not recommended for funding***

Total Scoring Data

Final Total Score: 65

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

Mean	66
Median	65
Standard Deviation	6
Highest	80
Lowest	60
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (1-84): Not recommended for funding	14

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	4	5	5
Is the rationale sound?	1	8	5
Is the proposal well planned and designed?	1	5	8
Is the proposal feasible?	0	6	8

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

Strengths
- This is a high-risk application and thus is relevant to this funding opportunity.
- They PI proposes a powerful humanized model for *in vivo* reprogramming of myofibers. This is a highly relevant alternative approach to iPSC studies and is worth pursuing.
- The experimental strategy is clearly written.

Concerns
- Although not emphasized in the title or specific aims, the application focuses on the use of the proposed strategy to promote regeneration in the context of DMD. This is a major flaw since this disease does not result from a defect in satellite cells but due to the lack of dystrophin. If the proposal were focused on aging, the rationale would have more merit.
- The provided preliminary data is unconvincing.
- The proposal is lacking novelty and impact.
- The proposal is not clearly written, goals are not well articulated, there is an excess of abbreviations that are never defined in the text and there are identical paragraphs on page 6.

DISCOVERY

Application #	DISC1-09991
Title (as written by the applicant)	Development of dual-gate chimeric antigen receptor therapy for lethal, stem-like neuroendocrine prostate cancer
Research Objective (as written by the applicant)	The objective is the development of a dual gate chimeric antigen receptor T cell (CAR-T) therapy for neuroendocrine prostate cancer (NEPC) with potent tumor killing and minimal off-tumor effects.
Impact (as written by the applicant)	If the research is successful, dual gate CAR-T for NEPC would represent targeted therapy with a favorable therapeutic index for a highly aggressive and deadly disease without standard therapies.
Major Proposed Activities (as written by the applicant)	• Develop and test CEACAM5/Trop2 dual gate CAR-T for selective cytotoxicity against neuroendocrine prostate cancer. • Assess combinations of CEACAM5/Trop2 dual gate CAR-T for preclinical evidence of cytotoxicity in vivo. • Evaluate the preclinical safety of CEACAM5/Trop2 dual gate CAR-T targeting neuroendocrine prostate cancer.
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	$221,858
GWG Recommendation	***Not recommended for funding***

Total Scoring Data

Final Total Score: 82

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

Mean	82
Median	82
Standard Deviation	4
Highest	90
Lowest	75
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	6
Tier 2 (1-84): Not recommended for funding	8

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	11	1	2
Is the rationale sound?	4	2	8
Is the proposal well planned and designed?	5	3	6
Is the proposal feasible?	3	2	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

- Neuroendocrine prostate cancer (NEPC) is highly aggressive with few options. NEPC represents an excellent model to test the investigator's hypothesis.
- The proposed work is highly significant as there is a clear need for better approaches to deal with therapy resistant prostate cancers, and solid cancers have been challenging for CAR-T applications.
- The proposed dual gate CAR-T cell approach is novel.
- The proposed dual gate strategy could have a dramatic impact in the use of CAR-T technology for treating cancer.
- Strengths of the proposal include the PI's leadership in the field of cancer cell antigen discovery and the work showing that CEACAM5 appears to be a specific target of NEPCs.
- The PI is an expert in prostate cancer.
- The resources at the institution are excellent.

Concerns

- CAR-T cells have not been successfully used in solid tumors. There is no discussion to suggest what the primary barriers might be and how these will be overcome with the proposed approach.
- The relevance of the proposal to stem cell biology is not clear.
- The presumed specificity of the construct for NEPC does not appear to avoid toxicity to normal tissues (although this will be studied).
- The PI has identified Trop2 expression as a potential target for iCARs, however it unclear whether a surface molecule that is more highly expressed on tumors rather than normal cells is a good way to ensure safety of the dual CAR-T approach.
- The PI does not consider the potential of bystander effects on cells expressing Trop2 affecting the ability of proper on-target function of anti-CEACAM5 CAR-T cells.
- Studies are limited to NEPC cell lines.
- Aims 2 and 3 are highly dependent on any success being made in Aim 1.

DISCOVERY

Application #	DISC1-09994
Title (as written by the applicant)	Zika Virus-induced Disturbances in Human Neural Stem Cell Mitosis and Migration: Role of Centrosomes and Microtubules
Research Objective (as written by the applicant)	Discover how Zika virus leads to brain defects in unborn fetuses to infected pregnant mothers by studying fetal-like brain stem cells and their protein machinery. Develop technologies to find drugs.
Impact (as written by the applicant)	No treatment exists for Zika virus. By testing human brain stem cells with Zika we propose to identify specific protein defects and discover potential drugs for treating brain-related birth defects.
Major Proposed Activities (as written by the applicant)	• Create brain (neural) stem cells and mini-brains in a dish from powerful embryonic-like pluripotent stem cells and then study how Zika blocks these stem cells from dividing and making new neurons. • Assess how Zika targets the cell division (mitosis) process as brain stem cells make new neurons, requiring complex protein machinery (centrosome) to closely coordinate the dynamics with chromosomes. • In a developing brain, neural stem cells need travel from their birthplace to their final position in the brain. Here we will study how Zika targets and disrupts the movement of brain stem cells. • Determine how Zika modifies brain stem cell protein function involved in movement and maintaining cell division, by tagging them with a phosphorylation mark, for developing drug-discovery assays. • Develop targets and a method that rescue the movement (migration) abnormalities of brain stem cells disrupted by Zika virus. • Develop an automated method for counting centrosomes during cell division (mitosis) in brain stem cells for discovering new compounds that normalize the disruptions by Zika virus.
Statement of Benefit to California (as written by the applicant)	Almost 35,000 cases of Zika virus outbreak have been reported in the U.S., including 2,800 pregnant women, 36 live-born infants with birth defects (2 in California), and 5 pregnancy losses. Although 400 travel-related infections have been reported in California, local mosquito-borne transmission could spread here. This is a sobering reminder for Californians that ZIKV can cause serious harm to a developing fetus. Therefore, studying ZIKV now and discovering a treatment has become imperative.
Funds Requested	$241,992
GWG Recommendation	***Not recommended for funding***

Total Scoring Data

Final Total Score: 60

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

Mean	59
Median	60
Standard Deviation	10
Highest	82
Lowest	30
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (1-84): Not recommended for funding	14

Score Influences

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

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

- Since Zika causes congenital microcephaly, the authors suggest that research attention should be focused on the pathways that influence brain development *in utero*. This is a reasonable approach to developing hypotheses for targeted research.
- Since there are few other promising paths to Zika therapies, even starting on a long road such as this is worthwhile. One must start somewhere and the basic hypothesis is sound.
- If the research successfully shows centromere or microtubule changes *in vitro* (and that these are causative and not merely correlative for disease), this system could be used for additional Zika research, including drug screening.

Concerns

- The science is interesting with respect to viral biology, but there is no indication of how this has therapeutic value.
- This research is basic biology. Any positive result would be very far from translation.
- It is unclear that looking at the effects of "pathways" in single cells will inform the cause of a gross anatomical dysmorphology. That said, hNSCs do enable this approach.
- There is not a lot of overlap between the Go Analysis (Fig 4) and the Ingenuity Pathway Analysis (Figure 5). This discrepancy should be explained.

DISCOVERY

Application #	DISC1-09999
Title (as written by the applicant)	Generation of expandable, self-renewing muscle stem cells for Duchenne Muscular Dystrophy
Research Objective (as written by the applicant)	The goal of this proposal is to define protocols to generate expandable, self-renewing human muscle stem cells (MuSC) from hiPS cells for Duchenne Muscular Dystrophy disease modeling and therapeutics.
Impact (as written by the applicant)	The integration of STAT3i with current approaches to derive myogenic cells from hiPS cells would enable the generation of self-renewing MuSC that are expandable for disease modeling and therapeutics.
Major Proposed Activities (as written by the applicant)	• Selection of the most potent STAT3i among three drugs extensively tested in preclinical and clinical studies. • Immunophenotyping of healthy and DMD hiPS-derived MuSC treated with STAT3i to assess cell identity. • Clonal analysis of healthy and DMD hiPS-derived MuSC treated with STAT3i to assess the composition of derived culture. • Gene expression profiling by RNAseq to compare healthy and DMD hiPS-derived MuSC treated with STAT3i with human MuSC isolated from patients. • Transplantation of healthy and DMD hiPS-derived MuSC in vivo into immunodeficient dystrophic mice.
Statement of Benefit to California (as written by the applicant)	Duchenne Muscular Dystrophy (DMD) is a lethal muscle wasting disease that affects 1:3500 males. This devastating disease is characterized by progressive loss of skeletal muscle and heart function. DMD affects more than 1,000 boys in California and poses a large economic burden for patients' families and society. Approaches to generate expandable human MuSC would be invaluable for the development of reliable disease modeling platforms as well as stem cell therapies to rescue disease progression.
Funds Requested	$265,500
GWG Recommendation	***Exceptional merit and warrants funding, if funds are available***

Total Scoring Data

Final Total Score: 85

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

Mean	85
Median	85
Standard Deviation	2
Highest	88
Lowest	80
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	9
Tier 2 (1-84): Not recommended for funding	5

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

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

- This proposal will address unmet needs and define protocols to generate expandable, self-renewing human muscle stem cells (MuSC) from hiPS cells for Duchenne Muscular Dystrophy disease modeling and therapeutics.
- An important therapeutic aspect of this proposal is that success could lead to the development of therapies for DMD and other muscle dystrophies.
- Experimental design is solid and is expected to produce meaningful outcomes.
- Three drugs that will be tested are approved and in use in preclinical studies.
- The PI is experienced.

Concerns

- In vivo experiments are in the mouse model. Mouse studies are unlikely to be sufficient for translation to clinic.
- This is a good application but it is not high risk, high reward.
- There is no novelty in generating expandable muscle progenitor cells from hiPS cells. This has been accomplished using another approach. Testing STAT3 inhibition is incremental.
- Although the research team has great expertise in muscle biology, there is no evidence they can recapitulate the proposed published protocol for generating myogenic cells from hPS cells. The whole application depends on this activity.
- There has been no scientific report documenting that cells generated using the proposed methodology possess *in vivo* regenerative potential.
- Lack of human ESC controls is a concern.
- It is unclear if the proposed doses of cells will be sufficient for repair.
- Previous studies indicate that low numbers of MuSCs can aid in repair. While more cells are usually better (especially for *in vitro* analysis) it is not clear if an increase in MuSCs is essential to heal damaged muscle in DMD patients.

DISCOVERY

Application #	DISC1-10001
Title (as written by the applicant)	Induction of immune tolerance of hESC-derived allografts using HLA-matched hESC-derived immune suppressive dendritic cells
Research Objective (as written by the applicant)	To develop immune suppressive dendritic cells derived from human embryonic stem cell (hESC) into a novel candidate to induce immune tolerance of HLA-matched hESC-derived allografts.
Impact (as written by the applicant)	Our proposed research will provide an effective and safe strategy to overcome the bottleneck of allogeneic immune rejection that hinders the clinical development of hESC-based therapy.
Major Proposed Activities (as written by the applicant)	• To differentiate genetically modified hESCs into immune suppressive dendritic cells, denoted DCcp • To fully characterize the immune suppressive properties of DCcp • To generate humanized mouse model reconstituted with human immune system, denoted Hu-mice • To test whether DCcp can induce immune tolerance of teratomas formed by HLA-matched unmodified hESCs in Hu-mice • To differentiate hESCs into cardiomyocytes and smooth muscle cells • To test whether DCcp can induce immune tolerance of cardiomyocytes and smooth muscle cells derived from HLA-matched hESCs in Hu-mice
Statement of Benefit to California (as written by the applicant)	hESC based cell therapy offers a unique opportunity to treat major diseases with limited therapeutic options, such as cardiovascular diseases (the leading causes of death and disability among Californians) and neural degenerative diseases (great burden on California medical care system). But one key bottleneck is the allogenic immune rejection of hESC-derived cells by recipients. Our proposed research is aimed to resolve this bottleneck and improve the feasibility of hESC-based cell therapy.
Funds Requested	$232,200
GWG Recommendation	***Not recommended for funding***

Total Scoring Data

Final Total Score: 75

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

Mean	77
Median	75
Standard Deviation	2
Highest	80
Lowest	75
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (1-84): Not recommended for funding	14

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	5	3	6
Is the rationale sound?	1	4	9
Is the proposal well planned and designed?	0	2	12
Is the proposal feasible?	1	2	11

Reviewer Comments

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

Strengths

- The proposal aims to generate tolerogenic PSC derived dendritic cells (DCs), by taking advantage of hESCs expressing CTLA4-Ig and PD-L1, which are well characterized tolerance inducing or immune-dampening molecules.
- The main strength of the proposal is the PI's track-record in the field of PSC function and applications.
- The experimental approach using the humanized mouse model addresses critical translatability issues of previous approaches: the fact that most immunosuppressive approaches work well in the mouse models but fail clinical trials.
- This is a novel and unique strategy for promoting immunological acceptance of SC-derived differentiated cells for regenerative medicine.
- There is strong discussion of potential pitfalls and alternative strategies.
- The resource sharing plan is a strength.

Concerns

- A major caveat and concern is the proposed use of CTLA4-Ig expressing PSC-derived DCs. CTLA4-Ig would not only act locally to induce tolerance, but it will likely act systemically inducing a prolonged and/or broad level of immune dysfunction in the host. This would make any therapy based on this approach not very likely to achieve the intended goals of specific tolerance induction. A key test of the above concern was proposed as part of Aim 2, in which PSCs that are not HLA matched to the cp-DCs will be implanted along with HLA-matched PSCs.
- Re-challenge with matched skin grafts or other tissues after allogeneic ES cell acceptance is necessary to demonstrate true immunological tolerance.
- The lack of strong preliminary data is a concern.
- There is concern that teratoma formation of not fully differentiated ES cells, which will be tolerated by the host, may be a risk for the patient.
- There is no data or discussion on what happens to DCcp after infusion. How long do they last? Since DCs are generally short-lived, why would transplant 7 days after treatment be effective if most DCs will be gone by then?
- In Figure 2b, if the mechanism is mediated by Tregs, which are CD4+, why aren’t they found in the teratomas?

DISCOVERY

Application #	DISC1-10014
Title (as written by the applicant)	Human Pancreatic Cancer Stem Cells: A Novel Way for Eradication
Research Objective (as written by the applicant)	We will use pancreatic cancer (PC) stem cells to show 1 inhibits proliferation, self-renewal and cell viability. MOA will be studied. This paradigm is transformational for anti-cancer drug discovery.
Impact (as written by the applicant)	Pancreatic cancer (PC) kills >40,000 in the US every year. PC remains a major medical unmet need. Use of PC stem cells in drug discovery of 1 will usher in a new therapeutic paradigm.
Major Proposed Activities (as written by the applicant)	• Show 1 reduces self-renewal capacity and cell viability of a pancreatic cancer stem cell and compare the result with a normal pancreatic cancer cell. • Show 1 induces apoptosis of a pancreatic cancer stem cell line via the intrinsic induced cell death (or apoptosis) pathway. • Show effectiveness of 1 as an inhibitor of the KRAS-NF-κB signaling pathway as a mechanism to eradicate pancreatic cancer stem cell progression. • Show effectiveness of 1 as an inhibitor of the ROS-dependent PTEN/PI3K/AKT/mTOR signaling pathway as a mechanism to eradicate pancreatic cancer stem cell progression. • Summarize the results in a report and apply for support to do additional IND-enabling studies.
Statement of Benefit to California (as written by the applicant)	We will develop a new pancreatic cancer (PC) therapy using PC cancer stem cells. In CA, the incidence of PC death is ~5,000/yr. PC incidence is increasing in CA and will be 20% greater in 2020. Therapy for PC is limited to surgery. Combinations of chemotherapy and radiation are ineffective. PC is a major unmet medical need. Successful completion of this work will provide citizens of CA much needed advances in PC health technology and improvement in health care and an effective anti-cancer drug.
Funds Requested	$303,894
GWG Recommendation	***Not recommended for funding***

Total Scoring Data

Final Total Score: 75

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

Mean	74
Median	75
Standard Deviation	4
Highest	85
Lowest	70
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	1
Tier 2 (1-84): Not recommended for funding	13

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	6	4	4
Is the rationale sound?	1	5	8
Is the proposal well planned and designed?	0	7	7
Is the proposal feasible?	1	3	10

Reviewer Comments

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

Strengths

- Pancreatic cancer is highly aggressive with few options. The novel agent appears to be potent against pancreatic cancer cells *in vitro* and *in vivo*.
- The studies are logically planned.
- The candidate drug acts on different pathways inducing apoptosis and inhibiting autophagy in cancer cells.
- The cancer cell models and the molecular biology methods for mechanistic interrogation for the pathway of action are adequate.
- The resources available appear to be adequate.

Concerns

- The proposed studies investigate the outcomes (apoptosis, autophagy) of treatment with the novel agent, but they do not identify its molecular mechanism.
- The studies of cancer stem cells utilize a single cell line that has not been validated for CSC properties.
- The tumor treatment data is not impressive, with very little important effects and no evidence provided of altered survival.
- Evidence to support claims of safety is very superficial.
- The PI does not have any publications relating to either pancreatic cancer or stem cell biology and will be reliant on the expertise of the co-investigators.
- The objectives of the proposal are not clearly outlined.
- The proposal is densely written, lacks clarity of approaches and is poorly organized.
- The non-specific effects of the drug cancer on normal stem cells is not studied or discussed.

DISCOVERY

Application #	DISC1-10017
Title (as written by the applicant)	Modeling Zika viral infection and congenital Zika syndrome in human neural stem cells
Research Objective (as written by the applicant)	The proposed studies will use human neural stem cells as a model to examine Zika virulence and related birth defects, explore the role of viral RNAi as an innate antiviral mechanism in development
Impact (as written by the applicant)	The proposed research will provide a better understanding of Zika and related birth defects, and potentially provide a viral RNAi-based therapeutic for the treatment of congenital Zika syndrome
Major Proposed Activities (as written by the applicant)	• Generate a precise map of viRNAs in the Zika genome, validate candidate viRNAs for their anti-Zika efficacy and therapeutic potentials to treat congenital Zika syndrome using human neural stem cells • Use human neural stem cells as a model system to establish Zika-host interaction network and pinpoint molecular mechanism responsible for the suppression of Dicer mediated host antiviral activity
Statement of Benefit to California (as written by the applicant)	Zika virus is now threading in California. The total number of Zika cases has increased from 6 to 459 in just about a year, and continues to climb. 71 infections were documented in pregnant women, and 3 babies were born with congenital Zika syndrome. Stem cells has become an invaluable model system to study Zika virulence and related birth defects, therefore the proposed study will offer unique biological insights for better understanding of the threat and potential development of therapeutics.
Funds Requested	$250,200
GWG Recommendation	***Not recommended for funding***

Total Scoring Data

Final Total Score: --

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

Mean	--
Median	--
Standard Deviation	--
Highest	--
Lowest	--
Count	13
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (1-84): Not recommended for funding	13

Score Influences

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

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

- *None noted*

Concerns

- The finding that Zika can affect Dicer has already been published. Similarly work on brain organoid development seems to already have been done by others.
- There is concern about the choice of cells to infect in light of the timing of the effects of Zika virus infection.
- The approach is not sound and even if all of the aims were successfully accomplished there would be minimal impact on the Zika field.

DISCOVERY

Application #	DISC1-10020
Title (as written by the applicant)	Identification of Human Spermatogonial Stem Cell-Specific Markers
Research Objective (as written by the applicant)	To use single-cell and genomics approaches to identify a set of genes that define human SSCs; i.e., a “SSC gene signature”
Impact (as written by the applicant)	The SSC signature defined in this proposal will be used 1) to purify and expand SSCs for clinical application and 2) serve as a SSC quality control monitor for reconstituting fertility in patients
Major Proposed Activities (as written by the applicant)	• To define gene expression profiles of human spermatogonia at single-cell resolution. • To identify human SSCs and their associated transcriptome signatures.
Statement of Benefit to California (as written by the applicant)	Over 1 million men in California suffer from major fertility deficiencies. This application is focused on new approaches for treating male infertility that revolve around using spermatogonial stem cells (SSCs). SSCs provide a source of germ cells for engendering fertility to patients undergoing cancer chemotherapy treatment. By expanding SSCs cryopreserved before such patients undergo chemotherapy, their fertility can later be restored by transplantation.
Funds Requested	$232,200
GWG Recommendation	***Not recommended for funding***

Total Scoring Data

Final Total Score: 60

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

Mean	59
Median	60
Standard Deviation	9
Highest	75
Lowest	30
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (1-84): Not recommended for funding	14

Score Influences

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

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

- This proposal will potentially address development of future infertility treatments for boys undergoing cancer treatment.
- Unclear how proposed RNAseq for putative SSCs can help to develop new therapies or improve existing cryopreservation approaches.
- No *in vivo* experiments are proposed to show that identified subsets are indeed SSCs.

Concerns

- Sperm and testicular tissue cryopreservation methods for preserving fertility for cancer survivors already exist.
- There is no reason that molecular markers for human spermatogonial stem cells are the limited factor in pushing the field forward.
- Target group of patients is small and not a high priority compared to many others.
- For Aim 1, the number of captured transcripts and the number of cells are two key parameters that are not discussed.

DISCOVERY

Application #	DISC1-10036
Title (as written by the applicant)	Prodrug innovation to target muscle stem cells and enhance muscle regeneration
Research Objective (as written by the applicant)	To target therapeutics to muscle stem cells, the building blocks of skeletal muscle.
Impact (as written by the applicant)	Drugs, genes and gene editing strategies can be delivered directly to muscle stem cells to alleviate disease.
Major Proposed Activities (as written by the applicant)	• Synthetic peptides based on the ectodomains of Myomaker will be synthesized, with a fluorophore conjugated for tracking. Alternatively, anti-Myomaker sdAbs will be developed to target MuSCs. • Peptides or sbAb from Activity 1 will be tested in vitro for binding against isolated mouse and human MuSCs, as well as other cell types to assess targeting specificity. • The optimized targeting moiety from Activity 2, will be delivered via intramuscular injection to a myotoxin-injured hindlimb muscle in mice to assess in vivo MuSC-targeting. • A prodrug will be synthesized by conjugating the optimized targeting moiety with SB202190, a drug known to rescue the regenerative capacity of aged MuSCs. • Bioactivity of the SB prodrug will be assessed in vitro in isolated mouse and human MuSCs, using known biomarkers including phosphorylation of p38α/β and MK2. • For clinical indications, the SB prodrug treatment will be tested in a mouse myotoxin-induced muscle injury model. Muscle regeneration and functional recovery will be assessed.
Statement of Benefit to California (as written by the applicant)	Skeletal muscles are critical for all voluntary movements. Muscle deterioration due to aging or genetic disorders often leads to grave physical disability and diminished quality of life. Combined, muscle disorders impose a significant economic burden of over $18B/year in the U.S. Currently, there exists no means of targeting muscle stem cells, the engines of muscle tissue growth and repair throughout life. We will meet this need and increase the efficacy and safety of muscle therapeutic agents.
Funds Requested	$235,834
GWG Recommendation	***Exceptional merit and warrants funding, if funds are available***

Total Scoring Data

Final Total Score: 86

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

Mean	87
Median	86
Standard Deviation	2
Highest	90
Lowest	85
Count	12
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	12
Tier 2 (1-84): Not recommended for funding	0

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	11	0	1
Is the rationale sound?	10	1	1
Is the proposal well planned and designed?	8	0	4
Is the proposal feasible?	9	0	3

Reviewer Comments

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

Strengths

- The study presents a novel approach to modulating repair of muscle in situ in aging and disease.
- This proposal is aimed at making an antibody or peptide for targeting drugs or other payload directly to human muscle stem cells and has the potential to be very high impact.
- Currently there are no ways of specifically targeting muscle stem cells. If successful, this project will pave the way.
- This is a high risk, high impact application.
- The rationale for this application is strong. The identification of a novel muscle stem cell specific cell surface marker TMEM8c/Myomaker is a fundamental first step for enabling this application.
- The novelty of the approach is a strength.
- The applicants have interesting preliminary data on pharmacological manipulation of muscle regeneration.
- It is expected that the assembled team will complete the proposed aims.

Concerns

- The mechanism whereby peptide mimetics will bind the target is not clearly elucidated; Figure 3 does not really illuminate this point.
- The impact of the study is strongly dependent upon whether the data in mice will be relevant to humans. Human studies on the drug indicate it blocks differentiation, and it is not clear if this is the key issue in aging muscle.
- It is not clear if this strategy will deliver sufficient concentration of drug at target *in vivo*.

DISCOVERY

Application #	DISC1-10058
Title (as written by the applicant)	Integrated approach for combined in situ gene and stem cell based therapy for urea-cycle disorders
Research Objective (as written by the applicant)	Develop a novel gene cum cell based therapy for liver pathologies that integrates in situ CRISPR based gene correction of hepatocytes with transplantable engineered vascularized liver tissues.
Impact (as written by the applicant)	An integrated gene cum cell transplantation therapy that results in a population of healthy liver cells to restore normal tissue function will create a new regenerative medicine paradigm.
Major Proposed Activities (as written by the applicant)	• iPSC gene correction and differentiation to healthy hepatocytes. • Engineering bioprinted vascularized liver tissues. • Metabolic characterization of engineered hepatic tissues. • In situ gene repair of diseased livers via CRISPR-AAVs. • In situ engineered vascularized hepatic tissue patch transplantation. • Evaluation of tandem cell and gene therapy regimens.
Statement of Benefit to California (as written by the applicant)	We believe our integrated approach of in situ gene correction coupled with autologous cell therapy aiming at the implantation of patient-specific, genetically modified tissues will have a significant impact in treating liver pathologies and improving the quality of life of patients. Findings and technologies developed from this study can be easily extended to a broad spectrum of liver pathologies and genetic diseases, thus having a potentially far-reaching socio-economic impact in the state.
Funds Requested	$232,200
GWG Recommendation	***Not recommended for funding***

Total Scoring Data

Final Total Score: 70

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

Mean	68
Median	70
Standard Deviation	8
Highest	80
Lowest	50
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (1-84): Not recommended for funding	14

Score Influences

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

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	4	3	7
Is the rationale sound?	2	3	9
Is the proposal well planned and designed?	0	4	10
Is the proposal feasible?	0	5	9

Reviewer Comments

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

Strengths

- This proposal will focus on developing gene and cell therapeutic approach for treatment of Ornithine Transcarbamylase Deficiency (OTC).
- The investigators have done substantial work engineering the bioprinter device and if successful could provide interesting data for generation of 3D vascularized tissue constructs.
- The PI track-record and collaborators are a major strength of this proposal, as are the exciting preliminary results showing small vascularized liver constructs, and AAV split Cas9 targeting results.

Concerns

- The significance and potential for impact are minimal.
- The proposal is very ambitious but not entirely novel.
- The aims are not well integrated and rationale and experimental design for them are unclear. The feasibility of the proposed research is questionable.
- It is unclear how feasible it would be to achieve the proper goals within the allotted time and budget.
- The work proposed in Aim 2 is clearly outlined. However, there is concern whether sufficient targeting and repair will be achieved *in vivo* to make the approach feasible.

DISCOVERY

Application #	DISC1-10071
Title (as written by the applicant)	Functionalized Nanoparticles in Direct Reprogramming of Human Fibroblasts to Functional Hepatocytes
Research Objective (as written by the applicant)	We will produce nanoparticles for reprogramming human skin cells into functional liver cells. The newly generated liver cells will be characterized and subsequently used for liver tissue regeneration.
Impact (as written by the applicant)	We propose safe autologous cell therapy for people with liver failure disorders using new healthy liver cells derived from patients' own skin cells that will restore normal liver function.
Major Proposed Activities (as written by the applicant)	• Specific AimGenerate functional hepatocytes by direct reprogramming of human fibroblasts using non-integrating biocompatible functionalized nanoparticles. • Generate non-integrating biocompatible nanoparticles functionalized with covalently linked hepatocyte-specific reprogramming factors. • Evaluate and optimize direct reprogramming efficiency of the functionalized nanoparticles based on hepatocyte-specific gene expression using real time RT-PCR, FACS and immunostaining. • Examine preservation of genome integrity by whole genome sequencing of original fibroblasts and niHep expressing hepatocyte-specific genes. • Characterize functional properties of hepatocytes reprogrammed directly from human fibroblasts upon treatment with non-integrating functionalized nanoparticles.
Statement of Benefit to California (as written by the applicant)	California citizens with liver failure disorders and/or in need for liver transplant will directly benefit from the personalized cure sought in the proposed research. By reducing the expensive costs of care for this debilitating disease and providing otherwise unavailable personalized liver tissue, it will reduce and/or eliminate detrimental consequences of liver diseases such as organ failure or liver cancer thereby impacting overall healthcare and insurance costs.
Funds Requested	$150,000
GWG Recommendation	***Not recommended for funding***

Total Scoring Data

Final Total Score: 60

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

Mean	60
Median	60
Standard Deviation	5
Highest	70
Lowest	45

Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (1-84): Not recommended for funding	14

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

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

Reviewer Comments

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

Strengths

- The technology for linking purified proteins to nanoparticles for reprogramming is interesting.

Concerns

- The proposal lacks novelty except for development of non-integrating nanoparticles with hepatocyte-specific reprogramming factors.
- The significance and potential for impact are moderate.
- The proposal has low potential for impact and is unlikely to yield interpretable results.
- Overall feasibility of the project is unclear.
- This proposal is based on a false premise that lentiviral vectors are genotoxic.
- The investigators appear to overplay the safety of their system.
- Direct programing may have merit, shortening of time period for reprograming may be an advantage. But investigators did not back this claim with data.
- All experiments are *in vitro* and unlikely to produce meaningful results on functionality of reprogrammed hepatocytes *in vivo*.

DISCOVERY

Application #	DISC1-10074
Title (as written by the applicant)	Reprogramming human stem cells for blood cell generation
Research Objective (as written by the applicant)	To create a universal donor blood cell line that can be used to produce human red blood cells for transplantation.
Impact (as written by the applicant)	Successful completion of this work would create a safe, unrestricted source of universal donor human blood cells that could be used to improve healthcare and save lives throughout the world.
Major Proposed Activities (as written by the applicant)	• Aim 1: Development of a human donor blood cell line by introduction of the appropriate signals into stem cells • Aim 2: Induce the human donor blood cell lines to produce red blood cells
Statement of Benefit to California (as written by the applicant)	Because this research will lead to the development of methods to address the critical shortage of universal donor blood for transfusions, the State of California and its citizens will directly benefit. California-based military personnel stationed elsewhere will also benefit from this resource. Importantly, in emergency situations, it will not be necessary to obtain blood test results to identify the recipient's blood type, thus expediting access to treatment and improving patient outcomes.
Funds Requested	$232,200
GWG Recommendation	***Exceptional merit and warrants funding, if funds are available***

Total Scoring Data

Final Total Score: 90

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

Mean	90
Median	90
Standard Deviation	0
Highest	90
Lowest	90
Count	13
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	13
Tier 2 (1-84): Not recommended for funding	0

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	11	0	2

Is the rationale sound?	11	0	2
Is the proposal well planned and designed?	11	0	2
Is the proposal feasible?	11	0	2

Reviewer Comments

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

Strengths

- The proposal focuses on the generation of red blood cell products and is significant.
- The strengths of the proposed work are the strong preliminary data, the PIs track record and the assembled collaborators, and the many alternative approaches and considerations provided in the application.
- The main concept is well supported by strong preliminary results showing that human erythroblast cells can be expanded from modified HSCs.
- Aim 1 is well supported, and the use of AAV nicely addresses previous concerns, and might even facilitate the final reticulocyte and RBC differentiation step.
- Aim 2 provides a nice set of *in vivo* functional and imaging based analyses that will provide clear evidence for the desired outcomes.
- The preliminary data are of high quality and convincing.
- The investigative team is experienced and well regarded.
- The proposed studies are within the technical expertise of the investigative team.
- Appropriate alternative strategies are discussed.
- The resources at the institution are excellent.
- The PI is very responsive to previous reviewers' comments. Consequently, the proposal is very much improved.

Concerns

- *None noted*

DISCOVERY

Application #	DISC1-10076
Title (as written by the applicant)	Transient gene activations for improved stem cell differentiation to endoderm and mature Human Hepatocytes
Research Objective (as written by the applicant)	To significantly improve differentiation of pluripotent stem cells to liver cells creating an expandable and efficient cell source.
Impact (as written by the applicant)	This work will significantly improve our ability to make human liver cells efficiently improving both disease studies and providing liver cells for human transplant.
Major Proposed Activities (as written by the applicant)	• To improve making endoderm, the immature cell type that can eventually become a mature liver cell. A secondary goal is to make endoderm directly expandable. • To improve final differentiation of mature liver cells. • To use RNA analysis to directly compare this new method to previous methods of making liver cells from stem cells. • To test the effectiveness of this new differentiation method, the differentiated cells will be transplanted into a model of liver failure in immunodeficient mice.
Statement of Benefit to California (as written by the applicant)	The proposed research will significantly improve our ability to generate cells that can lead to improved liver cells and pancreatic cells. This technology will significantly accelerate research in diseases using stem cells to help scientists develop targeted cures with small molecules. Finally this technology will improve our ability to expand and successfully transplant healthy liver cells.
Funds Requested	$149,999
GWG Recommendation	***Not recommended for funding***

Total Scoring Data

Final Total Score: 70

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

Mean	73
Median	70
Standard Deviation	5
Highest	85
Lowest	70
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	1
Tier 2 (1-84): Not recommended for funding	13

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	6	0	8
Is the rationale sound?	3	0	11
Is the proposal well planned and designed?	0	6	8
Is the proposal feasible?	0	3	11

Reviewer Comments

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

Strengths

- This proposal may improve the efficiency of the differentiation of iPSCs to endoderm and hepatocytes.
- The generation of hepatocytes is highly significant and current approaches have a range of limitations.
- The approach of regulating gene expression during the generation of iPSCs to create cells with improved engraftment and differentiation characteristics is sensible.

Concerns

- The significance and potential for impact is moderate.
- The translational potential of this work is uncertain.
- Insufficient detail is provided on experimental design and expected outcomes.
- It is unclear how just adding doxycycline at different times will improve differentiation.
- The transient expression idea is generally interesting. However, the choice of genes with universal roles rather than specific functional aspects of this differentiation limits the impact of the study and raises some concerns on the eventual state and usability of the cells (even with transient expression).

DISCOVERY

Application #	DISC1-10079
Title (as written by the applicant)	An exosome-based translational strategy to mitigate Alzheimer's disease neuropathology
Research Objective (as written by the applicant)	These studies will determine whether stem cell derived exosomes (nano-scale vesicles) can be used to treat the symptoms of Alzheimer's disease (AD).
Impact (as written by the applicant)	Our stem cell-derived exosome therapy will provide a viable approach to ameliorate the relentless progression of AD that severely impacts quality of life for millions of patients and their families.
Major Proposed Activities (as written by the applicant)	• Evaluate whether exosome therapy can reduce the symptoms of early stage AD including anxiety, depression, and learning and memory. • Evaluate whether exosome therapy can reduce the symptoms of advanced stage AD including anxiety, depression, and learning and memory. • Determine whether exosome therapy can slow the appearance of AD related changes typically observed in the early stage AD brain. • Determine whether exosome therapy can reduce the appearance of AD related changes typically observed in the advanced stage AD brain.
Statement of Benefit to California (as written by the applicant)	In the US, California has the most cases of AD, a burden on patients, their families, and the health care system. As such, AD is an unmet medical need that requires new therapies to improve disease management. This project tests a transformational idea—human stem cell derived exosome therapy. These studies will identify a novel stem cell-based strategy and a viable approach to impede the progression of AD and it's symptoms that severely impact quality of life for patients and their families.
Funds Requested	$179,911
GWG Recommendation	***Exceptional merit and warrants funding, if funds are available***

Total Scoring Data

Final Total Score: 85

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

Mean	86
Median	85
Standard Deviation	2
Highest	89
Lowest	85
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	14
Tier 2 (1-84): Not recommended for funding	0

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	12	0	2
Is the rationale sound?	9	0	5
Is the proposal well planned and designed?	6	1	7
Is the proposal feasible?	8	0	6

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

Strengths
- The significance and potential for impact is high. If successful, the proposal could pave the way for future AD therapy.
- The approach is a novel, innovative and important idea to test.
- Aims and experiments are well defined and feasible within the proposed timeline.
- The PI is an established radiation biologist with a solid research program.

Concerns
- Rationale is based on a recently published study in PNAS (2016) demonstrating the efficacy of hNSC-derived exosomes in ameliorating the effects of cranial irradiation in mice. However, it is uncertain whether similar approach will be effective for AD. Translational aspect is less certain as mouse model may not be adequate to understand human AD pathology and therapy.
- The research, if successful, may not advance the field very much. There will still be a long way to go towards full biological understanding and/or a therapy.
- The mouse models of AD are not very good, and it is not clear that any benefit in mice will translate to humans. However, this may be only way forward.
- The use of human derived exosomes in mice raises concerns about xenogeneic proteins and epitopes complicating the therapy and interpretation of results.
- Some of the differences in effect may be due to a bundle of xenogeneic proteins being delivered and stimulating an immune response. Perhaps this can be addressed with a better control arm.
- It is not clear as to how the project as proposed will allow translational strategies to mitigate AD neuropathy as the difference between causal and consequential gene regulation has not been addressed.
- The PI has limited experience and expertise in AD and stem cell research.

DISCOVERY

Application #	DISC1-10087
Title (as written by the applicant)	Therapeutic potential of human umbilical cord derived mesenchymal stem cells in neonatal bronchopulmonary dysplasia
Research Objective (as written by the applicant)	This project will test the paracrine therapeutic potential of human umbilical cord derived mesenchymal stem cells (hUC-MSCs) in amelioration of neonatal bronchopulmonary dysplasia (BPD).
Impact (as written by the applicant)	Treatment of BPD with hUC-MSC conditioned media is minimally invasive without the side effects of stem cell implantation, and could open application of this media in clinical trials of human BPD.
Major Proposed Activities (as written by the applicant)	• To identify the role of hUC-MSC conditioned media in protection of lung alveolar and vascular injury in an in vitro model of BPD. • To determine in vivo targets of hUC-MSC conditioned media action in amelioration of murine hyperoxia-induced neonatal BPD.
Statement of Benefit to California (as written by the applicant)	BPD is a chronic debilitating disease of premature infants with high morbidity and mortality. About 15,000 new cases of BPD occur annually in the US. It is the second most expensive childhood disease after asthma, costing $2.4 billion annually. Our preliminary work showed amelioration of murine BPD via injection of mouse mesenchymal stem cell conditioned media (MSC-CM). This work will test efficacy of human umbilical cord MSC-CM in murine BPD and gain insights into the mechanism of the disease.
Funds Requested	$202,680
GWG Recommendation	***Not recommended for funding***

Total Scoring Data

Final Total Score: --

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

Mean	--
Median	--
Standard Deviation	--
Highest	--
Lowest	--
Count	13
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (1-84): Not recommended for funding	13

Score Influences

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

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

Reviewer Comments

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

Strengths

- The proposal addresses an important unmet clinical need. Bronchopulmonary dysplasia has major long term sequelae and there is no current treatment.

Concerns

- This is not a high-risk, high-reward project and is not adequately focused on stem cell based research.
- The proposal lacks novelty. There is an extensive list of potential therapeutic effects for conditioned medium from mesenchymal cells and TGF beta signaling is well known to be involved in extracellular matrix remodeling.
- The concept of treating bronchopulmonary dysplasia with MSC is not novel; clinical trials are underway.
- The proposal lacks novelty regarding the overall concept and the experiments designed to look at mechanisms whereby MSC might exert a beneficial effect.
- There is no strong rationale provided for the use of umbilical cord MSC over other types of MSC.

DISCOVERY

Application #	DISC1-10096
Title (as written by the applicant)	Characterization of hCD47b mAb Anti-Melanoma Properties in the Immune-Humanized Mouse Model
Research Objective (as written by the applicant)	Our objective is to use patient matched hematopoietic stem cells to create immune-humanized in-vivo mouse model and test therapeutic antibodies against metastatic melanoma.
Impact (as written by the applicant)	Our studies will identify efficient therapeutic anti-melanoma regimen using stem cell based experimental platform that bridges laboratory animal model and human immune system.
Major Proposed Activities (as written by the applicant)	• To Evaluate melanoma antigens as therapeutic target in Immune-Humanized mouse models. We will reveal in-vivo anti-tumor effects of their blockade mediated by human myeloid and lymphoid cell lineages. • To Test the Synergy Between antibodies blocking melanoma antigens and T-Cell Check point Inhibitors using Metastatic Melanoma Immune humanized mouse model.
Statement of Benefit to California (as written by the applicant)	Successful completion of this project will create an in-vivo stem cell based platform for physiological testing and evaluation of the compounds capable of activating adaptive and innate cell effectors. Defining therapeutic action of blocking antibodies in this system will bring a unique form of cancer immunotherapy from lab to bedside to the citizens of the Sate of California.
Funds Requested	$202,680
GWG Recommendation	***Not recommended for funding***

Total Scoring Data

Final Total Score: 73

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

Mean	73
Median	73
Standard Deviation	2
Highest	75
Lowest	70
Count	13
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (1-84): Not recommended for funding	13

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	1	4	8

Is the rationale sound?	1	4	8
Is the proposal well planned and designed?	0	6	7
Is the proposal feasible?	2	2	9

Reviewer Comments

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

Strengths

- The proposal focuses on the treatment of melanoma.
- A strength of the proposal is the PIs recent work showing that CD47 is expressed at higher levels in metastatic melanoma cell lines and samples, and the preliminary data showing that blocking CD47 increases phagocytosis of these cell by macrophages.
- The resources at the institution are excellent.
- The use of the GMCSF and SCF modified NSG mouse for CD34+ transplantation is a good idea, and should help with the otherwise defect in myeloid function in standard NSG mice. The BLT mouse model is considered as an alternative.
- The PI provides careful consideration to the potential problems of using anti-CD47 treatments and gives alternative dosing treatments.

Concerns

- This proposal will examine the effects of blocking CD47 on human melanoma cells to treat metastatic outcomes using a humanized mouse model.
- The applicability to stem cells is limited to the use of human HSCs to develop a model to test CD47 cells. This may allow the interaction between macrophages and tumor cells, but it is unlikely that anti-tumor T cells will be present.
- Immuno-oncology is a crowded area.
- CD47 blocking antibodies are being studied by several companies.
- The investigator is relatively inexperienced in this field of research.
- The proposed work is focused on immune-therapeutic approaches, and not really aimed at understanding the cancer stem cell properties that lead to CD47 increased expression.
- The preliminary data showing a change in MDSC to macrophage ratio in anti-CD45 treated tumors are quite striking, and it is curious that the PI does not follow up on this finding.