INCEPTION AWARDS

$2,871,984 GWG RECOMMENDED

APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Previous CIRM Funding	Utility or Disease Target	Product Type to be Tested
DISC1-10603	iPSC-Derived Smooth Muscle Progenitors for Treatment of Abdominal Aortic Aneurysm	$172,621	**Y**	**92**	92	0	92	92	14	0	Y	Aortic anuerysm	Cell therapy
DISC1-10475	Generation of human airway stem cells by direct transcriptional reprogramming for disease modeling and regeneration	$238,408	**Y**	**90**	88	4	80	90	12	2	N	Respiratory diseases	In vitro disease model
DISC1-10643	IVD rejuvenation using iPSC-derived notochordal cells	$241,992	**Y**	**86**	87	2	85	90	11	0	N	Intervertebral disc degeneration	Cell therapy
DISC1-10598	Enhanced Branching Morphogenesis and Pluripotent Cell Lineage Differentiation for Pediatric Regenerative Therapies	$235,800	**Y**	**86**	86	4	80	90	10	4	Y	Kidney disease	Combination cell/scaffold therapy
DISC1-10583	Human Pancreatic Cancer Stem Cells: Developing a Novel Drug for Cancer Eradication	$303,894	**Y**	**86**	84	4	75	87	10	4	Y	Pancreatic cancer	Small molecule drug
DISC1-10555	Optimizing self-renewal signaling kinetics to stabilize ex vivo hematopoietic stem cell expansion	$235,836	**Y**	**85**	85	2	80	90	13	1	Y	Blood stem cell expansion	Cell maintenance system
DISC1-10620	Bone Marrow Targeting of Hematopoietic Stem Cells Engineered to Overexpress 25-OH-VD3 1-α-hydroxylase for Acute Myeloid Leukemia Therapy	$178,967	**Y**	**85**	85	0	85	85	14	0	N	Acute myeloid leukemia	Gene-modified cell therapy
DISC1-10513	Novel metabolic labeling method for tracking stem cells to irradiated salivary glands using PET	$235,613	**Y**	**85**	84	2	80	85	10	4	N	In vivo stem cell tracking	Cell labeling methodology
DISC1-10522	Identification of antigenic neo-epitopes from in vitro reprogrammed human tissue precursors for regenerative therapy	$193,500	**Y**	**85**	84	3	80	87	9	5	N	Immunogenicity of reprogrammed cells	Tool to assess immune rejection
DISC1-10588	Targeting cancer stem cells with nanoparticle RNAi delivery to prevent recurrence and metastasis of ovarian cancer	$172,870	**Y**	**85**	84	4	80	90	8	6	N	Ovarian cancer	Nanoparticle RNAi
DISC1-10721	An IPSC cell based model of macular degeneration for drug discovery.	$232,200	**Y**	**85**	84	3	75	85	12	2	Y	Age-related macular degeneration	Cell-based drug screening tool
DISC1-10516	Development of treatments to improve healing of ischemic wounds	$235,800	**Y**	**85**	81	6	70	88	8	6	N	Diabetic foot ulcers	Combination cell/scaffold therapy
DISC1-10718	Gingival mesenchymal stem cells as a novel treatment modality for periodontal tissue regeneration	$194,483	**Y**	**85**	78	14	40	85	8	6	N	Periodontitis	Combination cell/scaffold therapy
DISC1-10720	Regulation of pluripotency by Gremlin1	$232,200	**N**	**82**	81	9	55	90	7	7	N		
DISC1-10554	Modeling and Enhancing Mucociliary Clearance in Pulmonary Disease using Induced Pluripotent Stem Cells	$179,999	**N**	**80**	81	3	75	85	3	11	N		
DISC1-10641	Treating aplastic anemia using gene-edited autologous mesenchymal stem cells	$202,500	**N**	**80**	80	4	75	90	2	12	N		
DISC1-10725	Evaluating the functional integration of human pluripotent stem cell-derived kidney organoids in a mouse NOD/SCID transplant model	$250,200	**N**	**80**	80	5	70	90	3	11	Y		
DISC1-10480	Development of potent stem cell factors	$232,200	**N**	**80**	79	4	70	85	3	11	N		
DISC1-10557	Human iPSC-derived cortical neuron model of Huntington's Disease	$241,992	**N**	**80**	79	6	70	90	4	10	N		
DISC1-10674	A new phenotypic screening platform that identifies biologically-relevant targets and lead compounds for the treatment of Parkinson's disease	$150,000	**N**	**80**	79	5	70	85	3	11	N		
DISC1-10527	Label-free mechano-sorting of therapeutic cells derived from induced pluripotent stem cells	$180,000	**N**	**80**	78	2	75	80	0	14	N		
DISC1-10576	Human iPSC-Derived Liver-on-a-Chip Using Decellularized Extracellular Matrix	$202,414	**N**	**80**	78	9	60	90	6	8	N		
DISC1-10712	High Throughput Magnetic Assisted Transfection Platform for Manufacturing Hematopoietic Stem Cell and Induced Pluripotent Stem Cell Therapies	$145,125	**N**	**80**	78	7	60	85	1	13	N		
DISC1-10735	Loss of DNA 6-methyladenine (6mA) as a driver of self-renewal in myeloid leukemia stem cells	$180,000	**N**	**80**	78	6	70	90	1	13	Y		
DISC1-10499	Bone-healing cartilage derived from human pluripotent cells for the repair of large-scale bone injuries	$250,200	**N**	**80**	72	13	40	87	1	12	Y		
DISC1-10491	Manipulating integrins to dedifferentiate primary endothelial cells	$232,200	**N**	**79**	76	5	65	80	0	14	Y		
DISC1-10560	Leveraging post-transcriptional gene regulation to expand hematopoietic stem cells	$233,406	**N**	**75**	75	5	70	85	1	13	N		
DISC1-10634	CFIm25 inhibitors as a tool for improving somatic reprogramming efficiency	$208,544	**N**	**75**	75	0	75	75	0	14	N		
DISC1-10481	Stem cell gene therapy to cure muscular dystrophy	$235,836	**N**	**75**	74	6	65	85	1	13	Y		
DISC1-10622	Targeted degradation of the retinoblastoma protein for cell reprogramming and tissue regeneration	$171,700	**N**	**75**	74	10	45	84	0	14	N		

APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Previous CIRM Funding	Utility or Disease Target	Product Type to be Tested
DISC1-10612	Immune-compatible universal pluripotent stem cell-derived pancreatic islets graft for the cure of juvenile diabetes	$235,643	**N**	**70**	73	5	65	85	1	13	N		
DISC1-10529	Cochlear delivery of mesenchymal stem cell products for preventing drug-, noise-, and age-related deafness	$233,999	**N**	**70**	66	13	30	80	0	14	N		
DISC1-10615	Hiring bodyguards on the trip: Interaction between metastatic cancer stem cells and T regulatory cells	$180,000	**N**	**65**	66	7	60	85	1	13	N		
DISC1-10493	Self-renewal and differentiation defects hypothesized to arise in disease	$284,580	**N**	**65**	65	0	65	65	0	14	N		
DISC1-10581	Reprogramming of human pancreatic exocrine cells into beta-like endocrine cells	$231,248	**N**	**65**	58	16	10	80	0	14	N		
DISC1-10550	Directed Epigenetic Reprogramming for Cardiac Regeneration	$235,800	**N**	**62**	59	13	30	70	0	14	N		
DISC1-10716	Novel Acousto-Microfluidic Platform for Detecting Endothelial Progenitor Cells	$172,277	**N**	**-**	-	-	-	-	0	14	N		
DISC1-10506	Magnetic Nanoparticles as Mesenchymal Stem Cell Trackers	$102,582	**N**	**-**	-	-	-	-	0	14	N		
DISC1-10468	Age-related Reduction of Human Muscle-specific Stem Cells Limits Functional Recovery after Rotator Cuff Injury	$230,502	**N**	**-**	-	-	-	-	0	14	N		
DISC1-10673	Major Histocompatibility Complex (MHC) Class I expression during spontaneous differentiation of iPSCs.	$180,000	**N**	**-**	-	-	-	-	0	14	N		

CIRM 2.0 CALIFORNIA'S STEM CELL AGENCY

DISCOVERY

Application #	DISC1-10603
Title (as written by the applicant)	iPSC-Derived Smooth Muscle Progenitors for Treatment of Abdominal Aortic Aneurysm
Research Objective (as written by the applicant)	To assess the therapeutic effect of human induced pluripotent stem cell (iPSC)-derived smooth muscle progenitors (pSMCs) for treatment of abominal aortic aneurysm (AAA).
Impact (as written by the applicant)	Currently, there are no pharmacologic therapies for AAA. If successful, delivery of autologous pSMCs to the site of AAA will halt or reverse the progression towards a rupture-prone aneurysm.
Major Proposed Activities (as written by the applicant)	• Derive and characterize iPSC-derived pSMCs in vitro. • Deliver pSMCs to the abdominal aortic wall of mice with induced AAA. • Quantitatively assess pSMC survival non-invasively by bioluminescence imaing for up to 28 days. • Quantify the abdominal aortic diameter by ultrasound imaging for up to 28 days. • After 28 days, perform histological quantification of elastin content and pSMC cell survival. • Perform quantitative gene expression analysis of elastin expression.
Statement of Benefit to California (as written by the applicant)	We propose to generate human induced pluripotent stem cell-derived smooth muscle progenitors for treatment of abdominal aortic aneurysm (AAA). This stem cell-based therapy will benefit California by providing a new treatment for AAA. Production of these therapeutic cells at the clinical scale will provide job opportunities to citizens of California. The benefits of this new regenerative therapy will have a tremendous impact on the state of California and to patients suffering from AAA.
Funds Requested	$172,621
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

Scoring Data

Final Score: 92

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

Mean	92
Median	92
Standard Deviation	0
Highest	92
Lowest	92
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	0

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Will the proposed idea have impact on human stem cell research?	4	0	1
Is the scientific premise valid?	4	0	1
Is the experimental plan adequately designed to test the idea?	4	0	1

Is the proposed project duration appropriate?	3	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 presents a high risk/high reward project well aligned with the goals of the Inception program
- The use of iPSC-derived smooth muscle progenitors is an innovative approach toward treating and preventing abdominal aortic aneurysms
- The notion of delivering SMCs to aneurysm sites is logical and straightforward
- Characterization of histology and protein expression is strong
- The project has a good likelihood of success

Concerns

- Mechanical testing of the tissues would strengthen the analysis

DISCOVERY

Application #	DISC1-10475
Title (as written by the applicant)	Generation of human airway stem cells by direct transcriptional reprogramming for disease modeling and regeneration
Research Objective (as written by the applicant)	We will generate human airway stem cells by direct transcriptional reprogramming of fibroblasts. We will use these induced airway stem cells to model motile cilia disease in a dish.
Impact (as written by the applicant)	Generating airway stem cells through reprogramming will create a scalable and editable cell line from which we can derive airway epithelium, thus enabling airway disease modeling and drug screening.
Major Proposed Activities (as written by the applicant)	• Aim 1: Direct reprogramming of fibroblasts into human airway stem cells • Aim 2: Modeling motile cilia disease in reprogrammed human airway stem cells
Statement of Benefit to California (as written by the applicant)	More than 10% of Californians suffer from lung diseases such as COPD or asthma. Our proposed studies will attempt to directly convert skin cells into lung stem cells, facilitating the modeling of airway diseases in a dish. Disease modeling will lead to a deeper understanding of the cellular basis of airway diseases which could lead to novel drugs and regenerative therapies in the future, benefiting the people of California and beyond.
Funds Requested	$238,408
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

Scoring Data

Final Score: 90

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

Mean	88
Median	90
Standard Deviation	4
Highest	90
Lowest	80
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	12
(1-84): Not recommended for funding	2

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Will the proposed idea have impact on human stem cell research?	11	1	1
Is the scientific premise valid?	12	1	0
Is the experimental plan adequately designed to test the idea?	8	2	3
Is the proposed project duration appropriate?	9	0	4

Reviewer Comments

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

Strengths

- The group does not limit the proposal to cell therapy, they also propose to use the resulting product in disease modeling and drug screening, which collectively can have a significant impact on stem cell research
- “Bypassing” the iPS cell generation step by reprogramming the fibroblast with tissue-specific factors, thus generating a specific differentiated phenotype (airway cells), is novel and has been proven to be feasible in other systems
- The airway stem cell field needs innovation - this proposal will have an impact on stem cell research
- The proposal addresses an important cell type

Concerns

- Proof of concept studies are needed
- No mention of efficiency is concerning
- There are concerns regarding the number of cells that can be produced, mixed populations, and incomplete reprogramming without a good strategy to address these issues

DISCOVERY

Application #	DISC1-10643
Title (as written by the applicant)	IVD rejuvenation using iPSC-derived notochordal cells
Research Objective (as written by the applicant)	To identify a new therapeutic agent for disc regeneration using novel pluripotent stem cells and injectable beads that support differentiation and provide biomechanical strength.
Impact (as written by the applicant)	If this study is successful, we will be able to bring a completely new biologically and biomechanically relevant solution to degenerated intervertebral discs.
Major Proposed Activities (as written by the applicant)	• To optimize stem cell delivery, survival, differentiation and matrix secretion in an intervertebral disc (IVD) explant • To demonstrate the feasibility of stem cell regenerate intervertebral disc in a large animal model (pigs)
Statement of Benefit to California (as written by the applicant)	"My back hurts, Doc". It's one of the most common complaints heard by Californian family doctors. Traditional there is no good treatment today for disc degeneration. This study comes to promote future stem cell therapy for chronic back pain. Successful stem cell therapy will benefit all Californian residents by reducing workdays lose, medical costs and improving quality of life.
Funds Requested	$241,992
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

Scoring Data

Final Score: 86

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

Mean	87
Median	86
Standard Deviation	2
Highest	90
Lowest	85
Count	11
(85-100): Exceptional merit and warrants funding, if funds are available	11
(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
Will the proposed idea have impact on human stem cell research?	8	1	0
Is the scientific premise valid?	9	0	0
Is the experimental plan adequately designed to test the idea?	8	0	1
Is the proposed project duration appropriate?	7	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

- Excellent grant nearing clinical development
- May lead rather directly to intervertebral disc repair in vivo
- Excellent experimental design
- Large animal model experiments proposed are excellent
- Clear rationale and adequate experimental plan with a valuable feasibility study in a pig model

Concerns

- None indicated

DISCOVERY

Application #	DISC1-10598
Title (as written by the applicant)	Enhanced Branching Morphogenesis and Pluripotent Cell Lineage Differentiation for Pediatric Regenerative Therapies
Research Objective (as written by the applicant)	Approximately 20,000 babies are born annually with kidney disease; the long-term outcome is poor. These studies address new ways to develop mini-kidney structures for transplantation to induce repair.
Impact (as written by the applicant)	~85% of people on the organ waitlist are in need of a kidney and there are insufficient donors. There is a pressing need to identify methods for repair that avoid the need for an organ transplant.
Major Proposed Activities (as written by the applicant)	• Address a way to create mini-organs in 3D using growth factors, a biodegradable scaffold, and cell differentiation techniques that recapitulate kidney development and the required cell interactions. • Investigate the interactions between cells that induce each other by layering components and determining if structures needed are enhanced, and in a rigorous and reproducible manner. • Compare in a quantitative and qualitative manner the characteristic features required such as branching in layered 3D structures and the capabilities of cells to self-organize, interact, and mature. • Evaluate the effects of oxygen in the culture environment in which the cells and future mini-kidneys are grown to determine if the structures are enhanced and necessary vessels form. • Identify a candidate kidney construct with the necessary elements for future transplantation in a translational animal model of congenital kidney disease. • Publish the results and share outcomes on the CIRM and related websites.
Statement of Benefit to California (as written by the applicant)	Current data on the Organ Procurement and Transplantation Network show that across the U.S. 96,986 individuals are currently awaiting a kidney and there are only 17,155 donors in 2017, to date. For the State of California, 19,525 (~85%) are in need of a kidney. Of these ~250 represent children under 17 years of age. The studies in this proposal address the urgency in identifying solutions for repair and regeneration that will benefit the State of California and the youngest citizens in need.
Funds Requested	$235,800
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

Scoring Data

Final Score: 86

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

Mean	86
Median	86
Standard Deviation	4
Highest	90
Lowest	80
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	10
(1-84): Not recommended for funding	4

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Will the proposed idea have impact on human stem cell research?	11	0	2
Is the scientific premise valid?	9	1	3
Is the experimental plan adequately designed to test the idea?	8	2	3
Is the proposed project duration appropriate?	6	0	7

Reviewer Comments

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

Strengths

- The establishment of 3D kidney organoids with a biodegradable scaffold might provide a novel platform for the development of kidney repair approaches
- Great unmet need as kidney disease is common
- The proposal to develop kidney organoids for transplantation in pediatric renal failure is innovative and needed
- Construction of organoids in a biodegradable scaffold that ultimately could be placed in strategic anatomical sites with the intent of focal enhancements is reasonable
- The proposal and its successful completion would have a direct impact in the clinic and could indeed fulfill an unmet medical need
- The applicant has discussed strategies by which this first step can be eventually translated to clinical use
- Very strong application at all levels
- The proposal is well-designed, building on solid foundations and work already performed by the applicant in previous studies
- The team has extensive experience with kidney developmental biology

Concerns

- Would have been helpful to clearly define the limitations of a non-degradable scaffold
- There is no preliminary data comparing biodegradable scaffolds with decellularized kidneys
- There is no preliminary data to show that transduction of endothelial progenitors will not compromise their function
- The preliminary data show that iPSCs can proliferate on degradable scaffolds; however, they do not show any characterization of the cell types and structure after culture on scaffolds apart from SEM
- Not sure whether they achieved specific differentiation
- The scaffold has been published before

DISCOVERY

Application #	DISC1-10583
Title (as written by the applicant)	Human Pancreatic Cancer Stem Cells: Developing a Novel Drug for Cancer Eradication
Research Objective (as written by the applicant)	We will use human pancreatic cancer (PC) stem cells to show 1 inhibits proliferation, self-renewal and cell viability. This paradigm is transformational for anti-cancer drug discovery for patients.
Impact (as written by the applicant)	Pancreatic cancer (PC) kills >40,000/yr in the US. PC is a major unmet medical need. Use of PC stem cells in development of 1 will usher in a new paradigm. 1 may be of great utility with other drugs.
Major Proposed Activities (as written by the applicant)	• Show 1 potently and selectively reduces self-renewal capacity and cell viability of a human pancreatic cancer stem cell and compare the result with a normal pancreatic cancer cell. • Show 1 induces apoptosis of a human 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 human pancreatic cancer stem cell progression relevant to human patients. • Summarize the results in a pre-IND report and contact the U.S. FDA. Apply for financial 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 California, the incidence of PC death is ~5,000/yr. PC incidence is increasing in CA & will be 20% greater in 2020. Therapy for PC is limited to surgery. Combination of chemotherapy & radiation are ineffective. Thus, PC is a major unmet medical need. Successful completion of this work will provide CA citizens much needed advances in PC health technology & improvement in health care & effective anti-cancer drugs.
Funds Requested	$303,894
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

Scoring Data

Final Score: 86

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

Mean	84
Median	86
Standard Deviation	4
Highest	87
Lowest	75
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	10
(1-84): Not recommended for funding	4

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Will the proposed idea have impact on human stem cell research?	9	0	4
Is the scientific premise valid?	7	1	5
Is the experimental plan adequately designed to test the idea?	7	2	4

Is the proposed project duration appropriate?	5	1	7

Reviewer Comments

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

Strengths

- High-reward application
- Well-written proposal from an outstanding group
- Strong group with solid track record

Concerns

- Not transformational
- Cellular model is not entirely relevant; primary pancreatic organoid would be more interesting

DISCOVERY

Application #	DISC1-10555
Title (as written by the applicant)	Optimizing self-renewal signaling kinetics to stabilize ex vivo hematopoietic stem cell expansion
Research Objective (as written by the applicant)	We aim to develop conditions for stable expansion of blood stem cells outside of the body
Impact (as written by the applicant)	Blood stem cells are a rare but necessary cell type for curative bone marrow transplantation and related gene therapies. Stable blood stem cell expansion will increase therapy availability and success
Major Proposed Activities (as written by the applicant)	• Validate a fully defined all-recombinant protein culture system for long-term HSC expansion • Develop pharmacological strategies to provide robust ex vivo human HSC maintenance and expansion
Statement of Benefit to California (as written by the applicant)	Blood stem cell availability is a major bottleneck in bone marrow transplantation, a curative therapy for numerous blood diseases. Blood stem cells currently cannot be stably maintained outside the body. Stable culture conditions would therefore increase blood stem cell availability, and improve accessibility to clinical bone marrow transplantation and related gene therapies. This research will ultimately improve bone marrow transplantation and related gene therapies for patients in California.
Funds Requested	$235,836
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

Scoring Data

Final Score: 85

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

Mean	85
Median	85
Standard Deviation	2
Highest	90
Lowest	80
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	13
(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
Will the proposed idea have impact on human stem cell research?	12	0	1
Is the scientific premise valid?	8	1	4
Is the experimental plan adequately designed to test the idea?	7	3	3
Is the proposed project duration appropriate?	7	2	4

Reviewer Comments

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

Strengths

- A strong scientific premise and research strategy
- ex vivo expansion of HSCs would be a good advance if improved

Concerns

- Some concern was expressed about mouse data translating to human studies
- It is not clear why cord blood was not emphasized

DISCOVERY

Application #	DISC1-10620
Title (as written by the applicant)	Bone Marrow Targeting of Hematopoietic Stem Cells Engineered to Overexpress 25-OH-VD3 1-α-hydroxylase for Acute Myeloid Leukemia Therapy
Research Objective (as written by the applicant)	We propose a new approach to differentiation therapy for acute myeloid leukemia by producing local level of high-dose vitamin D in bone marrow via cell therapy with engineered hematopoietic stem cells
Impact (as written by the applicant)	If proven successful, the proposed research can serve as a major breakthrough in the treatment of multiple subtypes of AML and particularly important for improving survival in older patients.
Major Proposed Activities (as written by the applicant)	• Evaluate homing and expansion of engineered hematopoietic stem cells in bone marrow of human leukemic xenograft (HLX) mice after precondition with 5-Azacytidine • Optimize the number of injected hematopoietic stem cells without causing hypercalcemia • Determine if the local concentration of vitamin D3 is sufficient to differentiate leukemic blasts in bone marrow • Determine the efficacy of combination therapy of 5-Azacytidine and cell therapy by measuring overall survival • Determine the efficacy of combination therapy of 5-Azacytidine and cell therapy by measuring leukemia burden • Monitor serum calcium level from peripheral blood during treatment period
Statement of Benefit to California (as written by the applicant)	Acute myeloid leukemia (AML) has poor outcome, especially in older, ailing patients who can't tolerate aggressive conventional chemotherapy. If proven successful, our work can serve as a major breakthrough in the treatment of multiple subtypes of AML and particularly important for improving survival in older patients. The State of California will be a leading authority in this field. Further, this work will benefit patients around the world, not limited citizens of California
Funds Requested	$178,967
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

Scoring Data

Final Score: 85

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

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

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Will the proposed idea have impact on human stem cell research?	10	0	1
Is the scientific premise valid?	8	1	2
Is the experimental plan adequately designed to test the idea?	8	2	1
Is the proposed project duration appropriate?	5	0	6

Reviewer Comments

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

Strengths

- The approach to use stem cells to deliver vitamin D as an AML therapeutic is very innovative
- The proposal is supported by strong proof-of-concept data
- High impact if successful

Concerns

- It is unclear whether a sufficient number of stem cells exists in the marrow to generate sufficient vitamin D concentrations to have a therapeutic effect

DISCOVERY

Application #	DISC1-10513
Title (as written by the applicant)	Novel metabolic labeling method for tracking stem cells to irradiated salivary glands using PET
Research Objective (as written by the applicant)	This project aims to develop a sensitive and non-invasive method for tracking stem cells in clinical trial, without the need for genetically engineered reporters or long-lived radioisotopes.
Impact (as written by the applicant)	The ability to see follow stem cells over time, as they engraft, will make it possible to predict response to stem cell therapy and understand why treatments fail, when they do.
Major Proposed Activities (as written by the applicant)	• Synthesis and in vitro evaluation of 18F-tetrazine as a PET probe for tracking metabolically labeled stem cells • Cell tracking of metabolically labeled human salivary stem cells to monitor tissue regeneration in a mouse model of radiation-induced xerostomia
Statement of Benefit to California (as written by the applicant)	Regenerative cell-based therapies have shown promising results for a variety of diseases, including radiation-therapy-induced xerostomia, yet practical methods for tracking transplanted cells are still lacking. This project will develop a new method for labeling sensitive stem cells without the need for genetic engineering or long-lived radionuclides. This new tool will benefit Californians by accelerating progress toward cures in ongoing CIRM-sponsored trials of stem cell therapies.
Funds Requested	$235,613
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

Scoring Data

Final Score: 85

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

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

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Will the proposed idea have impact on human stem cell research?	11	0	3
Is the scientific premise valid?	8	2	4
Is the experimental plan adequately designed to test the idea?	7	3	4
Is the proposed project duration appropriate?	7	0	7

Reviewer Comments

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

Strengths

- The premise is innovative and likely to be effective
- Highly innovative - important for stem cell transplantation
- Innovative technology
- Important application for cell-based therapy
- Novel technology for cell monitoring and strong expertise in place
- The plan to evaluate the technology in vitro and in vivo is detailed and comprehensive
- Initial concerns were positively addressed

Concerns

- The key roadblock in tracking stem cells in vivo is longevity of signal; the label persistence will limit the ability to monitor the cells long-term and there is concern that improvements over existing technologies will not be observed
- The technology will only be able to assess engraftment of the cells
- Duration of the probe is too limited for long-term study
- Duration of cell monitoring is a concern
- Duration of the probe when stem cells differentiate is a concern

DISCOVERY

Application #	DISC1-10522
Title (as written by the applicant)	Identification of antigenic neo-epitopes from in vitro reprogrammed human tissue precursors for regenerative therapy
Research Objective (as written by the applicant)	This study examines potential immunologic changes caused by cellular reprogramming that could present a barrier to clinical application of regenerative therapies.
Impact (as written by the applicant)	Identification and evaluation of immunologic changes caused by cellular reprogramming provides critical information to maximize the efficacy and safety of regenerative cellular therapies.
Major Proposed Activities (as written by the applicant)	• Identify changes to the repertoire of endogenous MHC-presented peptides defining immunologic "self" in human hepatocytes reprogrammed from skin fibroblast-derived iPSCs. • Classify the mechanistic origins of reprogramming-induced neo-antigens using complimentary computational approaches. • Test the functional consequences of identified reprogramming-induced neo-antigens using in vitro assays of human T cell function.
Statement of Benefit to California (as written by the applicant)	This research has the potential to benefit the State of California and its citizens by contributing to the knowledge of reprogramming cells with the goal of developing new curative therapies for disease. The proposed research is aimed at improving the safety and efficacy of regenerative cellular therapies.
Funds Requested	$193,500
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

Scoring Data

Final Score: 85

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

Mean	84
Median	85
Standard Deviation	3
Highest	87
Lowest	80
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	9
(1-84): Not recommended for funding	5

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Will the proposed idea have impact on human stem cell research?	7	4	2
Is the scientific premise valid?	8	2	3
Is the experimental plan adequately designed to test the idea?	8	2	3
Is the proposed project duration appropriate?	7	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

- An important question that needs to be addressed
- Concept is very important - new exciting science
- Good team and good experimental design

Concerns

- Hepatocytes might not be the best cell type for this study
- Too much focus on hepatocytes, may be not the best population - cardiac cells might be better

DISCOVERY

Application #	DISC1-10588
Title (as written by the applicant)	Targeting cancer stem cells with nanoparticle RNAi delivery to prevent recurrence and metastasis of ovarian cancer
Research Objective (as written by the applicant)	Our objective is to develop novel treatments for women with ovarian cancer, specifically treatments that target stem cells to reverse drug resistance. These will treat recurrent metastatic disease.
Impact (as written by the applicant)	We aim to use nanoparticles to make ovarian cancer stem cells more drug sensitive, less invasive, and less likely to regrow tumors and metastasize.
Major Proposed Activities (as written by the applicant)	• Nanoparticles that can switch off genes that produce cancer stem cells will be tested to determine if they are an effective treatment for ovarian cancer. • We will use several cancer stem cell-associated proteins to deliver the nanoparticles precisely to the tumor. The most effective one will be advanced. • In our mouse model (human ovarian cancer cells growing in the ovaries of mice) we will compare standard chemotherapy with the nanoparticle therapy for effect on tumor size and spread. • We will identify genes that are turned on and off to produce ovarian cancer stem cells and the particular effect these genes have on how the cancer stem cells function. • By studying which genes are active with each candidate therapy, we will understand how they affect cells, define which one pinpoints the stem cells best, and discover other potential targets to study.
Statement of Benefit to California (as written by the applicant)	In California, there were 2310 ovarian cancer diagnoses, and 1530 deaths, in 2014. Over 70% of diagnosed ovarian cancers will recur and those that do, rarely respond to treatment. Our studies will use a novel nanoparticle method to protect and deliver therapy precisely to tumors. We are targeting molecules to cancer stem cells specifically, focusing on well-established factors. Our studies will advance a new therapeutic toward clinical trials for treatment of patients with this deadly disease.
Funds Requested	$172,870
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

Scoring Data

Final Score: 85

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

Mean	84
Median	85
Standard Deviation	4
Highest	90
Lowest	80
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	8
(1-84): Not recommended for funding	6

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Will the proposed idea have impact on human stem cell research?	12	0	1
Is the scientific premise valid?	8	2	3
Is the experimental plan adequately designed to test the idea?	7	3	3
Is the proposed project duration appropriate?	5	0	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 potential impact of the project is very high since ovarian cancer has few effective treatments
- The project is well-designed to test the premise of inhibiting EMT as a cancer treatment
- Strong in every category
- Potentially highly impactful, but high risk
- High impact

Concerns

- The novelty of the delivery technology is relatively low
- There is concern about feasibility of the delivery system

DISCOVERY

Application #	DISC1-10721
Title (as written by the applicant)	An IPSC cell based model of macular degeneration for drug discovery.
Research Objective (as written by the applicant)	Towards a cure for age related blindness, we propose to create a human stem cell based model to screen for drugs that are protective against age-related macular degeneration (AMD).
Impact (as written by the applicant)	With up to 11 million people in the United States affected by AMD, effective treatments against macular degeneration could address vision loss in millions of people.
Major Proposed Activities (as written by the applicant)	• Using stem cells engineered with disease relevant mutations, we will generate reporter stem cells that will allow us to visualize in the lab a major feature of age related macular degeneration. • We will study these cells to identify new biomarkers of the disease. • We will screen a library of drugs that are already approved FDA approved for other applications in an effort to find drugs that could be quickly repurposed for AMD.
Statement of Benefit to California (as written by the applicant)	The number of people with age-related macular degeneration in the US is roughly 11 million. And with 12% of the US population, that means that ~ 1.3 million individuals in California have some form of macular degenerative disease. Aside from the associated health care costs and loss of work, macular degeneration poses a serious quality of life for Californians. Developing new therapeutics for AMD here in California could provide new jobs to the local economy and bolster the biotech industry.
Funds Requested	$232,200
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

Scoring Data

Final Score: 85

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

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

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Will the proposed idea have impact on human stem cell research?	12	0	1
Is the scientific premise valid?	12	0	1
Is the experimental plan adequately designed to test the idea?	6	1	6
Is the proposed project duration appropriate?	5	0	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

- Use of iPS cells to generate the pathological model is highly innovative
- The proposal may identify drugs that impact retinal pathology

Concerns

- The hypothesis and language in the proposal could be more focused and specific

DISCOVERY

Application #	DISC1-10516
Title (as written by the applicant)	Development of treatments to improve healing of ischemic wounds
Research Objective (as written by the applicant)	We aim to develop an angiogenic proteoglycan mimic that will protect tissue from rapid degradation, and in conjunction with EPCs promote angiogenesis in order to accelerate ischemic wound healing.
Impact (as written by the applicant)	As a treatment, LXW7-DS-SILY combined with a collagen scaffold and EPCs will accelerate healing of ischemic diabetic foot ulcers and reduce limb amputation and mortality rates of diabetic patients
Major Proposed Activities (as written by the applicant)	• Aim 1. Synthesize and characterize the angiogenic potential of LXW7-DS-SILY • Aim 2. Quantify the effect of LXW7-DS-SILY and EPCs delivered with a 3D collagen scaffold on ischemic wound repair in a 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.
Funds Requested	$235,800
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

Scoring Data

Final Score: 85

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

Mean	81
Median	85
Standard Deviation	6
Highest	88
Lowest	70
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	8
(1-84): Not recommended for funding	6

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Will the proposed idea have impact on human stem cell research?	8	1	2
Is the scientific premise valid?	8	3	0
Is the experimental plan adequately designed to test the idea?	6	4	1
Is the proposed project duration appropriate?	6	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

- Great clinical impact
- The proposal addresses both issues of MMP activity degrading collagen and inducing formation of functional vessels using a novel tissue-engineering approach
- The promotion of an environment in which MMP-dependent matrix and growth factor degradation is reduced, while key building blocks for angiogenesis (EPC) are brought to the field “effortlessly” constitutes a solid proposition
- The proposal contains a combination of factors to overcome existing biological limitations responsible for current therapeutic failures
- Proposal contains appropriate controls, statistical analysis and alternative approaches in case of facing challenges
- Strong biomaterials approach - really well written proposal
- Preliminary data are provided to support the hypothesis that LXW7-DS-SILY protects collagen-based tissues and scaffolds, stimulates endothelial cells, and the composite material supports keratinocyte attachment

Concerns

- The phenotype of the EPC needs to be defined
- There is no evidence that EPCs will form functional vessels - suggest using adult cells

CIRM 2.0 CALIFORNIA'S STEM CELL AGENCY

DISCOVERY

Application #	DISC1-10718
Title (as written by the applicant)	Gingival mesenchymal stem cells as a novel treatment modality for periodontal tissue regeneration
Research Objective (as written by the applicant)	To develop a novel regenerative and adhesive hydrogel encapsulating patient's' gingival stem cell which can potentially be used as an adhesive dental hydrogel for periodontal tissue regeneration.
Impact (as written by the applicant)	Upon successful completion, this project will introduce a promising treatment approach for maxillofacial defects presenting an innovative treatment modality for periodontal tissue regeneration.
Major Proposed Activities (as written by the applicant)	• Utilizing human gingival mesenchymal stem cells (GMSCs) as a promising source for periodontal tissue regeneration. • To optimize the physiomechanical properties of the visible-light curable adhesive hydrogel for GMSCs encapsulation. • To engineer light curable hydrogel loaded with GMSC/HAp microparticles aggregates or TGF-β3 growth factor for periodontal tissue regeneration in vitro. • To optimize and determine the functionality of GMSCs-hydrogel system via relevant animal model.
Statement of Benefit to California (as written by the applicant)	Periodontitis is a prevalent chronic destructive inflammatory disease affecting tooth-supporting tissues in humans. Approximately 50% of Americans have some form of periodontal diseases. In this proposal, we aim to engineer a novel regenerative and adhesive hydrogel containing patient's' gingival stem cell aggregates/hydroxyapatite microparticles and growth factor, which can potentially be used as an adhesive dental hydrogel for periodontal tissue regeneration.
Funds Requested	$194,483
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

Scoring Data

Final Score: 85

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

Mean	78
Median	85
Standard Deviation	14
Highest	85
Lowest	40
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	8
(1-84): Not recommended for funding	6

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Will the proposed idea have impact on human stem cell research?	11	1	2
Is the scientific premise valid?	6	4	4
Is the experimental plan adequately designed to test the idea?	5	5	4
Is the proposed project duration appropriate?	5	1	8

Reviewer Comments

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

Strengths

- If the applicants can complete the proposed work successfully, they will have created/introduced a novel treatment modality for periodontal tissue regeneration
- Importantly and of great clinical relevance, this system can be dispensed with a syringe and cured using a dental curing light unit available in every dental practice
- Innovative technology
- Based on this very strong preliminary data and track record, it is possible to envision that this new technology for periodontal tissue repair will emerge from the successful completion of this project and soon be available to patients
- Given the multi-component nature of periodontitis, the use of adult stem cells (locally harvested in this case) may provide a more comprehensive therapeutic effect, based on the established activities of the cells in various of those components (osteoblast-dependent bone formation, immunomodulatory and anti-bacterial)
- The applicants have already demonstrated their ability to generate functional periodontal and bone tissue in in vitro and in vivo animal models using GMSCs derived from patients and recently provided the first demonstration that GMSCs have antibacterial properties against periodontitis causing bacteria
- The milestones are well-described and feasible

Concerns

- The applicants do not discuss pitfalls and possible setbacks
- There are concerns about immune responses with no potential pitfall/alternative approaches presented by the applicant
- Experimental plan lacks essential details and in-depth consideration of the risks
- Overambitious
- Limit the goals; the plan is overambitious

DISCOVERY

Application #	DISC1-10720
Title (as written by the applicant)	Regulation of pluripotency by Gremlin1
Research Objective (as written by the applicant)	To understand how the secreted protein Gremlin1 (GREM1) coordinates and integrates signaling in the extracellular media to regulate hESC pluripotency and differentiation.
Impact (as written by the applicant)	Validation of GREM1 as a regulator of pluripotency will provide insight into cell communication, hESC differentiation potential, and accelerate the rate at which hESCs can be used therapeutically.
Major Proposed Activities (as written by the applicant)	• Aim 1) Study the role of GREM1 in hESC/iPSC transition from pluripotency to DE. • Aim 1a. CRISPR/Cas9 to study the effects of CER1 on hESC pluripotency and DE formation. • Aim 1b. Biochemical characterization of GREM1 on hESC function. • Aim 2) Determine which GREM1 protein-protein interactions regulate pluripotency. • Aim 2a. Identify GREM1 binding sites on BMP-2, BMP-4, and SLIT1 and generate selective disruptor peptides. • Aims 2b and 2c . Explore the role of BMP-2 and BMP-4 in maintenance of pluripotency and explore the role of the SLIT1-GREM1 interaction on inhibition of SDF1α/CXCR4 signaling during DE formation.
Statement of Benefit to California (as written by the applicant)	Impact of proposed studies. Validation of GREM1 as a regulator of hESC pluripotency and definitive endoderm (DE) formation will provide new insight into how cells communicate with the extracellular environment, provide answers about differentiation potential, and generate new peptide-based tools that can be used to regulate directed hESC differentiation. Together, the findings will accelerate the rate at which hESCs can be applied to treat human disease.
Funds Requested	$232,200
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 82

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

Mean	81
Median	82
Standard Deviation	9
Highest	90
Lowest	55
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	7
(1-84): Not recommended for funding	7

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Will the proposed idea have impact on human stem cell research?	7	0	5
Is the scientific premise valid?	8	1	3
Is the experimental plan adequately designed to test the idea?	6	3	3
Is the proposed project duration appropriate?	8	0	4

Reviewer Comments

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

Strengths

- The research could indirectly impact treatments if it improved either the efficiency of self-renewal during expansion of PS cells, and potentially, to improve the efficiency of differentiation to any tissue
- The methodology used for screening is established, efficient, and high throughput

Concerns

- The proposal does not have a clear impact on therapies, but may provide improved stem cell culture and differentiation methods that could accelerate the development of new therapies
- Not clear how results will improve growth or differentiation of hPSC or provide advance over existing methodologies
- The application does not clearly enunciate the role of CER and GREM in hPSC maintenance and differentiation, and it is unclear which of these proteins is the focus of the study
- Preliminary data is correlative, no causative relationship is established
- Application would be stronger with knockdown studies in Aim1 as preliminary data
- Off target effects or likely potency issues should be considered
- Justification for study of SLIT pathway is unclear

DISCOVERY

Application #	DISC1-10554
Title (as written by the applicant)	Modeling and Enhancing Mucociliary Clearance in Pulmonary Disease using Induced Pluripotent Stem Cells
Research Objective (as written by the applicant)	To explore if over-activation of airway basal stem cells and their ciliated cell progeny are responsible for worsening lung diseases associated with dysfunctional mucociliary clearance.
Impact (as written by the applicant)	Bronchiolization is associated with several lung diseases with excessive mucus and impaired clearance. Our work offers potential new targets against airway basal stem cell activation.
Major Proposed Activities (as written by the applicant)	• Directed differentiation of iPSCs to airway basal stem cells and ciliated progeny from gain-of-function MUC5B (mucin producing gene) promoter variant cell lines. • Generation of mucociliary epithelium in transwells layered with functionalized barium alginate. The epithelium is later released by disintergrating the barium alginate. • Released mucociliary epithelium curls around itself and resembles the spinning sloughed-off epithelium or detached polyps in MUC5B gain-of-function promoter variant in IPF. • Functional assays to understand the role of spinning ciliated polyps in regulating mucin composition and disease progression. • Identifying potential targets and pathomechanims involved in bronchiolization using differential gene expression analysis.
Statement of Benefit to California (as written by the applicant)	Every individual at some point has most likely encountered challenges in mucociliary clearance (MCC), such as the common cold to more severe devastating conditions such as chronic obstructive pulmonary disorder. Despite its clinical importance, targeting bronchiolization, a pathological finding associated with MCC has never been attempted. We will use iPSC banked at CIRM for our studies in order to identify targets to enhance MCC.
Funds Requested	$179,999
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 80

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

Mean	81
Median	80
Standard Deviation	3
Highest	85
Lowest	75
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	3
(1-84): Not recommended for funding	11

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Will the proposed idea have impact on human stem cell research?	8	1	4
Is the scientific premise valid?	6	3	4
Is the experimental plan adequately designed to test the idea?	4	7	2
Is the proposed project duration appropriate?	6	1	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 approach to utilize an in vitro model for mucociliary clearance is innovative and potentially transformative in enabling systematic study of this disease
- This is an interesting approach with the goal to better understand related pulmonary diseases and possible future drug discovery
- This proposal does indeed address an unmet need which takes into account the fact that there are no adequate models to address this issue or to test novel therapeutic approaches
- Strong scientific premise
- The project has clearly designed experiments and milestones to evaluate the idea
- Taking into account the vast amounts of work already performed by the applicant in this field and their track record of several important discoveries, the outcome of their project could have fundamental and potentially far reaching consequences
- Solid track record of previous achievements

Concerns

- There is concern that the in vitro model may not adequately recapitulate the in vivo bronchiole microenvironment
- No comparison with previous models
- This proposal has no in vivo validation, which represents a major weakness and one that is difficult to overlook
    - In the current proposal, the applicants have stated that that there are no known human models or that human models currently available are inadequate to test their findings
    - Of note is that they have expressly stated that murine models are not appropriate for these studies as they lack airway basal cells (ABSCs) in the distal airways
- The applicant is planning to use three lines of iPSCs (WT, homozygous and heterozygous) but does not propose any knock-down, siRNA or any other means of blocking or downregulating the gain-of-function, as genetically suppressed lines may have different dynamics (compensatory mechanisms) that could be markedly different
- Given that only three of the tested seven samples revealed the gain-of-function mutation in the MUC5B promoter and no explanation or alternatives are provided for, the presence of pathology in the remaining four samples is a major caveat of the proposed study

DISCOVERY

Application #	DISC1-10641
Title (as written by the applicant)	Treating aplastic anemia using gene-edited autologous mesenchymal stem cells
Research Objective (as written by the applicant)	The objective is to explore feasibility of using gene-edited autologous mesenchymal stem cells to treat aplastic anemia. Specific aims are human MSC gene editing and engraftment in animal models.
Impact (as written by the applicant)	Proof of concept of MSC-based gene therapy platform for treating aplastic anemia patients with a mutant THPO gene, and other indications in which MSC can be used as a gene delivery vehicle.
Major Proposed Activities (as written by the applicant)	• Establish time course of human MSC engraftment in mouse models. hMSCs will be transplanted by intra-bone injection. Engraftment will be analyzed at 6, 10, 16, 20, 24, 32, 40 and 50-weeks. • Using our proprietary genome editing technology, normal THPO will be inserted and expressed in THPO defective-hMSCs to restore THPO activity. • Gene edited MSC-THPO will be tested for THPO activity using established cell-based assay.
Statement of Benefit to California (as written by the applicant)	Aplastic anemia (AA) is a serious and potentially life-threatening hematopoietic disorder. About 20-30% of AA patients are refractory to the current available treatments. More effective treatment options are therefore urgently needed. This proposal on using gene-edited, autologous mesenchymal stem cells to treat AA is in line with the CIRM mission. If successful, it will help California to maintain its leading role in accelerating stem cell treatments for patients with unmet medical needs.
Funds Requested	$202,500
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 80

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

Mean	80
Median	80
Standard Deviation	4
Highest	90
Lowest	75
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	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
Will the proposed idea have impact on human stem cell research?	8	2	2
Is the scientific premise valid?	5	4	3
Is the experimental plan adequately designed to test the idea?	5	4	3
Is the proposed project duration appropriate?	5	1	6

Reviewer Comments

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

Strengths

- The applicant proposes to use gene editing to restore the function of a rare gene mutation in aplastic anemia in patient MSC
- The novelty is the use of their proprietary gene editing tool; engraftment is a problem but they propose to use an approach whereby hMSCs are administrated by intra-bone marrow transplantation (IBMT)
- The idea of combining the gene-editing capabilities developed by the authors with the tissue targeting capacity of MSC (as vehicles) to deliver a specific therapy is novel, transformational and clearly worth testing
- The use of gene-editing tools is gaining significant momentum at a pre-clinical stage (potentially clinical soon) due to their specificity, efficiency and reproducibility
- Strong scientific premise

Concerns

- As a proof of concept model there is no in vivo approach that can be tested in mice
- Engraftment only works in mice, not sure how this translates to humans
- Proposed delivery hard to see as feasible in clinical settings
- Experimental plan is not cohesive
- Not sure where milestone 2 goes if transplanted normal hMSCs do not make or secrete THPO upon transplantation
- Aim two depends on the success of aim one
- The limitations of using THPO or mimetic for this disease should be discussed
- It would have been interesting to see alternative approaches in case of unexpected issues/failures

DISCOVERY

Application #	DISC1-10725
Title (as written by the applicant)	Evaluating the functional integration of human pluripotent stem cell-derived kidney organoids in a mouse NOD/SCID transplant model
Research Objective (as written by the applicant)	We will perform transplant studies to determine whether human stem cell-derived kidney organoids functionally integrate into the mouse kidney.
Impact (as written by the applicant)	Kidney disease affects 10% of the US population. A kidney transplant is the only curative solution to kidney loss. Kidney organoid transplants could identify a new approach to treat kidney disease.
Major Proposed Activities (as written by the applicant)	• Utilize a genetically engineered human stem cell line to generate kidney organoids. • Examine markers of normal human kidney development, organization and function in kidney organoids pre-grafting. • Graft human kidney organoids into immune-compromised mouse strains to evaluate graft-host integration. • Image human kidney organoid graft activity in the living kidney through specialized imaging approaches. • Following vital imaging, characterize 3D organization and cellular composition of the human kidney organoid transplant to determine appropriate structure and connectivity. • Detailed sub-cellular analysis of specialized cell types within human kidney organoid grafts to evaluate functional properties of implanted kidney cells.
Statement of Benefit to California (as written by the applicant)	The goal of our work is to develop approaches to treat kidney disease. Given that over 10% of the US population has some degree of kidney disease, this means millions of California residents. In fact, the problem is worse in California with a higher rate of kidney disease in the Hispanic population. Clearly, new therapeutic avenues could have a major benefit to the California populous.
Funds Requested	$250,200
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 80

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

Mean	80
Median	80
Standard Deviation	5
Highest	90
Lowest	70
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	3
(1-84): Not recommended for funding	11

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Will the proposed idea have impact on human stem cell research?	6	3	3
Is the scientific premise valid?	9	3	0
Is the experimental plan adequately designed to test the idea?	8	2	2
Is the proposed project duration appropriate?	6	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

- Very important step for cell based therapy in the kidney
- Well-presented proposal
- The proposal addresses an important application
- Strong group

Concerns

- Not entirely novel
- Not novel
- Lack of functional validation is a major limitation

DISCOVERY

Application #	DISC1-10480
Title (as written by the applicant)	Development of potent stem cell factors
Research Objective (as written by the applicant)	The goal of this research is to develop bioactive signaling proteins that are employed in the generation of mature and therapeutically viable cell types derived from human pluripotent stem cells.
Impact (as written by the applicant)	This work will impact research involving human pluripotent and adult stem cells by providing highly potent signaling proteins that influence stem cell behavior, including growth and differentiation.
Major Proposed Activities (as written by the applicant)	• We will engineer and produce proteins that have potent effects on stem cells, including pluripotent and adult stem cells. • We will generate antibody-like molecules that recognize critical stem cell surface biomarkers. • We will characterize the biochemical properties of the newly generated stem cell factors and antibody-like molecules. • We will characterize the effects of the newly generated stem cell factors on human pluripotent stem cells.
Statement of Benefit to California (as written by the applicant)	A major goal of pluripotent stem cell research is to derive cell types suitable for transplantation into individuals with chronic disorders in which tissues are damaged, diseased or dead. Successful completion of the proposed research will yield important tools that will facilitate the derivation of mature and therapeutically viable cell types. These tools will be valuable to biomedical researchers in academia and industry and will benefit patients in need of novel stem cell-based therapies.
Funds Requested	$232,200
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 80

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

Mean	79
Median	80
Standard Deviation	4
Highest	85
Lowest	70
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	3
(1-84): Not recommended for funding	11

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Will the proposed idea have impact on human stem cell research?	6	4	3
Is the scientific premise valid?	7	2	4
Is the experimental plan adequately designed to test the idea?	4	2	7
Is the proposed project duration appropriate?	6	0	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

- Will have a generally positive impact on stem cell differentiation research
- Targeted proteins are important factors to grow and to differentiate stem cells

Concerns

- Alternative approaches are available
- Non-canonical protein signaling not well addressed
- The non-canonical protein pathway needs to be considered
- Dose response might not be possible with engineered proteins

DISCOVERY

Application #	DISC1-10557
Title (as written by the applicant)	Human iPSC-derived cortical neuron model of Huntington's Disease
Research Objective (as written by the applicant)	Here we propose that cortical neurons derived from adult-onset HD patient iPSCs will recapitulate key phenotypes and generate a new iPSC-based HD model.
Impact (as written by the applicant)	This research would provide the preliminary evidence (substantiated HD phenotypes in human at-risk tissues) to generate a platform for further disease mechanism elucidation AND drug-discovery.
Major Proposed Activities (as written by the applicant)	• Cortical differentiation of adult-onset HD iPSCs. • Evaluation of morphological phenotypes in adult-onset HD iPSC-derived cortical neurons. • Evaluation of electrophysiological phenotypes in adult-onset HD iPSC-derived cortical neurons. • Evaluation of transcriptomic phenotypes in adult-onset HD iPSC-derived cortical neurons.
Statement of Benefit to California (as written by the applicant)	Huntington's disease (HD) is a fatal autosomal dominant neurodegenerative disorder affecting over 30,000 people in the US, with another 150,000 currently at risk. Our strategy proposes to use patient iPSCs differentiated into the cortical neurons lost in disease as a potential drug discovery platform and/or novel cell replacement therapy for HD, thus greatly benefiting the residents of the State of California.
Funds Requested	$241,992
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 80

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

Mean	79
Median	80
Standard Deviation	6
Highest	90
Lowest	70
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	4
(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
Will the proposed idea have impact on human stem cell research?	8	2	2
Is the scientific premise valid?	3	5	4
Is the experimental plan adequately designed to test the idea?	3	6	3
Is the proposed project duration appropriate?	5	0	7

Reviewer Comments

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

Strengths

- There is a strong rationale for studying cortical cells in HD, and not solely focus on striatal cells which, because they show massive degeneration in this disease context, have been the main target of research for decades
- The use of cortical derived iPSCs offers a novel model and constitute and valuable addition to the field to develop HD treatments and accelerate drug discovery
- The work provides an in vitro platform of iPSC-derived cells that are relevant for HD pathology
- The proposal is based on extending the analysis of neuronal damage in HD to cortical iPSC derived neurons, which are understudied in HD
- The field of HD research needs a cortical patient-derived iPSC model
- The scientific premise and experimental plan are strong

Concerns

- Benefit is unclear but understanding of the complexity of HD will be enhanced
- Strong specific hypotheses is desired
- The proposal does not mention or address the main culprit of this disease, that is the mutant Huntington protein
- Studying cortical cells in isolation, that is not in connection with striatal cells, is an important omission/flaw
- The expectation that cortical neurons provide novel and more therapeutically relevant information is not well justified
- The applicant does not address how or why the expected drug targets will be different from what has been identified using striatal-cell models
- Not clear whether the transcriptome analysis of cortical neurons adds a new aspect to understanding HD, i.e whether "new" disregulated gene sets that represent better therapeutic targets compared to striatal HD neurons will be identified
- Neurite length of HD neurons is only decreased when compared to low repeat controls but not in comparison to high repeat controls; while the applicant interprets this as the "assay being highly sensitive" one could argue that the assay does not pick up HD specific defects
- The rationale and readout needs to be improved; dendrite length measurements are a very basic measure
- Would like to see discussion of the importance of striatal-cortical interactions, perhaps as a future aim

DISCOVERY

Application #	DISC1-10674
Title (as written by the applicant)	A new phenotypic screening platform that identifies biologically-relevant targets and lead compounds for the treatment of Parkinson's disease
Research Objective (as written by the applicant)	Demonstrate that our HitFinder™ library can be screened for phenotypic changes in A53T-IPSC-derived dopaminergic neurons and use a secondary handle to identify the targets responsible.
Impact (as written by the applicant)	This technology combines phenotypic screening and target-ID eliminating the need to bias assays and/or screening libraries permitting application directly in iPSC-derived cells.
Major Proposed Activities (as written by the applicant)	• Prepare screening library including purchase of compounds and addition of chemical handles for target identification • Screen library for phenotypic changes in iPSC-derived engineered A53T-synuclein dopaminergic neurons: single point followed by dose-response • Large-scale preparation of compound-target complex in A53T IPSC-DA-neurons under conditions of phenotypic assay and confirm phenotypic change for target-ID. • Process scaled-up A53T-DA neurons and attach an affinity tag to the compound-target complex. Identify number of targets that reacted with the ligand (selectivity) and the identity of these targets.
Statement of Benefit to California (as written by the applicant)	This technology has the potential for broad impact on patients. Immediately, compounds and targets identified from this screen can progress into a drug discovery program to identify new treatments for Parkinson's disease (PD). PD is estimated to affect 36-60,000 Californians. Application of iPSC-derived neurons permits screening in patient-derived cells to determine if therapeutics/targets are relevant in all forms of PD (genetic and sporadic) and eventually expand to other diseases.
Funds Requested	$150,000
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 80

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

Mean	79
Median	80
Standard Deviation	5
Highest	85
Lowest	70
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	3
(1-84): Not recommended for funding	11

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Will the proposed idea have impact on human stem cell research?	10	1	2
Is the scientific premise valid?	4	3	6
Is the experimental plan adequately designed to test the idea?	3	3	7
Is the proposed project duration appropriate?	5	0	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 approach the applicant proposes might yield new potential drug candidates
- Approach and idea are not novel but potentially powerful
- New candidate drugs might benefit patients
- The envisioned work has a high chance of identifying a novel, candidate drug for PD and could fulfill an unmet need for a therapeutic agent for PD and new models for the quick screening of potential drugs using patient specific iPSCs
- This proposal is rigorous in its approach to perform high-throughput screening of a large number of compounds with possible therapeutic effects in PD
- The applicants carefully discuss all problems that this field has faced to this day and have actually properly tackled several of these issues
- Solid scientific premise
- Innovative

Concerns

- It is unclear how this is different from other high-throughput small molecule screening strategies and platforms
- It is unlikely that a single drug approach will "cure" PD but partial disease alterations are also useful
- Concern about using an unvalidated technology for pharmaceutical discovery
- There needs to be a positive control for an untested technology (which is the first hypothesis); applicant needs to demonstrate that this screening approach can identify compounds in a well-studied system, such as cardiac arrhythmias
- The main goal of this proposal to assess "the utility of [the technology] in phenotypic screening and target-ID" is incompatible with the secondary goal "to measure the effects of compounds on A53T-SYN-DA neurons"
- This is a largely a descriptive grant based on the production of clinical-grade cell lines

DISCOVERY

Application #	DISC1-10527
Title (as written by the applicant)	Label-free mechano-sorting of therapeutic cells derived from induced pluripotent stem cells
Research Objective (as written by the applicant)	To develop a technology to efficiently and accurately separate therapeutic cells from potentially harmful cells in a cost-effective manner.
Impact (as written by the applicant)	It will facilitate the therapeutic applications of stem cell-derived products by improving yield and efficiency from current multi-step, cell-function compromising processes.
Major Proposed Activities (as written by the applicant)	• Develop a cell culture/sorting system by optimizing electrical components and assembling into a high throughput format. • Test the capability and accuracy of the cell culture/sorting system by using individual stem cell products or in mixture.
Statement of Benefit to California (as written by the applicant)	This project seeks to advance the safety and effectiveness of the use of stem cells for regeneration of damaged tissues in patients by developing a novel technology. The project speaks directly to the mission of CIRM, particularly to improve human health of California's rapidly growing population by improving stem cell-based therapies. The commercialization of the full-scale system would benefit the people in California with the financial impact of increased employment and tax revenues.
Funds Requested	$180,000
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 80

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

Mean	78
Median	80
Standard Deviation	2
Highest	80
Lowest	75
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Will the proposed idea have impact on human stem cell research?	6	3	3
Is the scientific premise valid?	6	2	4
Is the experimental plan adequately designed to test the idea?	3	4	5
Is the proposed project duration appropriate?	5	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

- The use of piezeolectric forces to selectively detach cells is a novel approach toward cell purification

Concerns

- There is concern how cell-cell interactions will enable purification in high density cultures
- There is no preliminary data that different cell lineages will detach differently
- The project lacks a clear test-bed to evaluate effectiveness of the approach

DISCOVERY

Application #	DISC1-10576
Title (as written by the applicant)	Human iPSC-Derived Liver-on-a-Chip Using Decellularized Extracellular Matrix
Research Objective (as written by the applicant)	To develop dECM-based fibrotic liver model-on-a-chip by 3D printing, use microfluidic perfusion to model fibrotic liver lobule and study the hepatic functions and drug-induced hepatotoxicity.
Impact (as written by the applicant)	The success of this project will provide a functional fibrosis liver model to study patient-specific hepatic cell phenotypic and functional changes as well as their drug-induced hepatotoxicity.
Major Proposed Activities (as written by the applicant)	• Develop and optimize the decellularization protocol for porcine liver and characterize liver dECM with comparison to native liver. • Functionalize liver dECM for light-based polymerization to 3D print constructs for supporting human iPSC-derived hepatic cells • Develop dECM-based constructs with a stiffness gradient that matches the fibrotic liver microenvironment. • Incorporate a sinusoidal flow to the dECM-based liver fibrotic model with a stiffness gradient by 3D printing on a microfluidic chip. • Characterize the hepatic structure and functionality of iPSC-derived hepatic cells and compare them with those of liver cells in diseased conditions. • Study the drug metabolism and drug-induced hepatotoxicity of human iPSC-derived hepatic cells cultured on the fibrosis-model-on-a-chip.
Statement of Benefit to California (as written by the applicant)	Chronic liver diseases and cirrhosis are a major cause of death in California and the United States. Liver cancer, primarily in the form of hepatocellular carcinoma (HCC), is the second leading cause of cancer mortality in the world. This proposal aims to develop a hiPSC based liver model to understand the mechanisms of HCC progression in patients. The development of the 3D bioprinting technology and advanced biomaterials will keep California in the leading position in this emerging field.
Funds Requested	$202,414
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 80

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

Mean	78
Median	80
Standard Deviation	9
Highest	90
Lowest	60
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	6
(1-84): Not recommended for funding	8

Score Influences

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

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Will the proposed idea have impact on human stem cell research?	9	2	1
Is the scientific premise valid?	7	2	3
Is the experimental plan adequately designed to test the idea?	8	4	0
Is the proposed project duration appropriate?	5	1	6

Reviewer Comments

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

Strengths

- Innovative approach
- Very sound scientific premise; lots of potential impact, with weaknesses recognized
- Important applications for drug screening and toxicology especially in the context of nonalcoholic fatty liver diseases
- Good bioengineering plans

Concerns

- Novelty is limited
- No experimental details on how hepatocyte differentiation will be conducted
- No plans to validate functionality of final cells
- Highly risky

DISCOVERY

Application #	DISC1-10712
Title (as written by the applicant)	High Throughput Magnetic Assisted Transfection Platform for Manufacturing Hematopoietic Stem Cell and Induced Pluripotent Stem Cell Therapies
Research Objective (as written by the applicant)	Develop a transfection and cell reprogramming platform to accelerate and scale manufacturing of HSC and iPSC based therapies
Impact (as written by the applicant)	Realization of this technology would enable scale up & scale out manufacturing of HSC and iPSC therapies without the need for a large GMP facility. Instead therapy production can be deployed locally.
Major Proposed Activities (as written by the applicant)	• Pathway 1: Determine protein pattern and chip geometry for efficient attachment of adherent peripheral blood mononuclear cells (PBMCs) • Pathway 1: Quantify platform transfection efficiency and reagent consumption of GFP plasmid and virus for adherent PBMCs • Pathway 1: Compare micropillar magnetofection with traditional magnetofection and conventional co-incubation transfection methods for adherent PBMCs • Pathway 2: Determine chip geometry for efficient magnetic capture and arraying of CD 34+ HSCs • Pathway 2: Quantify transfection efficiency and reagent consumption for GFP plasmid and virus with CD34+ HSCs • Pathway 2: Compare micropillar magnetofection with traditional magnetofection and gold standard incubation transfection methods
Statement of Benefit to California (as written by the applicant)	This proposal has been submitted by a California company whose goal is to develop and commercialize a platform to accelerate manufacture of HSC and iPSC therapies. Many Californians can benefit from such a technology especially if deployed into underserviced communities, thereby bringing transformative therapies within reach of communities that need them the most.
Funds Requested	$145,125
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 80

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

Mean	78
Median	80
Standard Deviation	7
Highest	85
Lowest	60
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	1
(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
Will the proposed idea have impact on human stem cell research?	8	1	4
Is the scientific premise valid?	7	3	3
Is the experimental plan adequately designed to test the idea?	3	7	3
Is the proposed project duration appropriate?	8	1	4

Reviewer Comments

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

Strengths

- The 2D magnetic focusing technology described here is novel and innovative, with the potential to improve DNA delivery
- Could substantially drop cost and increase logistics - fundamentally enabling all kinds of applications that are currently too slow or too expensive or require specialized facilities
- Novel proprietary technology

Concerns

- The linkage to specific challenges in stem cell science and translation in unclear
- The project description lacks a detailed plan to develop and improve the technology
- The applicant needs to provide the proper positive and negative controls; please use other transfection techniques (e.g. electroporation, other magnetotransfection methods) on same cells with the new technology for head-to-head comparison
- The applicant needs to incorporate good statistics or power calculations, i.e. number of repeats of each measurement required to achieve desired statistical power; determine how confidence of a certain level of transfection has been achieved

DISCOVERY

Application #	DISC1-10735
Title (as written by the applicant)	Loss of DNA 6-methyladenine (6mA) as a driver of self-renewal in myeloid leukemia stem cells
Research Objective (as written by the applicant)	The research program outlined in this proposal is designed to reveal mechanisms of deregulated self-renewal and clonal malignancy in clinically intractable cases of acute myeloid leukemia.
Impact (as written by the applicant)	Our approach seeks to identify previously unrecognized targets for the expedited development of next-generation therapeutic strategies targeted against leukemic stem cells.
Major Proposed Activities (as written by the applicant)	• Aim 1. Define the function of DNA 6mA in murine leukemic stem cells. • Aim 2. Determine the impact of increased 6mA on self-renewal of human leukemic blasts.
Statement of Benefit to California (as written by the applicant)	Results from these studies will reveal mechanisms underlying clonal malignancy through deregulated self-renewal of immature myeloid leukemia blast cells. We anticipate that these studies will uncover promising therapeutic strategies against clinically intractable forms of myeloproliferative disease.
Funds Requested	$180,000
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 80

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

Mean	78
Median	80
Standard Deviation	6
Highest	90
Lowest	70
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	1
(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
Will the proposed idea have impact on human stem cell research?	7	2	4
Is the scientific premise valid?	3	5	5
Is the experimental plan adequately designed to test the idea?	4	4	5
Is the proposed project duration appropriate?	4	1	8

Reviewer Comments

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

Strengths

- This proposal may provide a novel strategy for treating leukemia and expansion of normal stem cells
- Project could impact on treatment of AML
- Published and preliminary data strongly support the hypothesis that regulation of methylation will prevent AML blast expansion
- Interesting preliminary data on the role of 6mA in AML; strong preliminary data to support involvement of this pathway

Concerns

- More detailed methods would be helpful
- Not clear in quantitative terms how much increase in 6mA is required to eliminate activity or how sustainable this needs to be
- More description of expected results and interpretation would be helpful
- Not exactly clear how a therapy would be delivered

DISCOVERY

Application #	DISC1-10499
Title (as written by the applicant)	Bone-healing cartilage derived from human pluripotent cells for the repair of large-scale bone injuries
Research Objective (as written by the applicant)	To test that a new stem cell therapy that can be used to generate substantial bone in the context of injury.
Impact (as written by the applicant)	Yearly 5 million patients suffer from severe bone injuries that require surgical intervention. Upon successful completion we will submit a DISC2 to develop a new cell therapy to repair these injuries.
Major Proposed Activities (as written by the applicant)	• We test that a special cell type derived from pluripotent cells can generate new bone rapidly and robustly. • We determine if the newly generated bone derived from implanted pluripotent cells is enduring and of high quality in an animal model.
Statement of Benefit to California (as written by the applicant)	The state of California has a large population of workers and aging citizens who suffer from skeletal injuries that cause pain, stress, and economic hardship. Our new stem-cell based strategy could revolutionize how large bone injuries are treated in the clinic leading to more rapid repair and significantly improved patient outcome.
Funds Requested	$250,200
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 80

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

Mean	72
Median	80
Standard Deviation	13
Highest	87
Lowest	40
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	1
(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
Will the proposed idea have impact on human stem cell research?	5	3	4
Is the scientific premise valid?	5	5	2
Is the experimental plan adequately designed to test the idea?	3	6	3
Is the proposed project duration appropriate?	4	2	6

Reviewer Comments

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

Strengths

- Using iPS-like cells to generate chondrocytes is interesting and novel
- The approach is novel and potentially impactful

Concerns

- Overall, the proposal was difficult to read and understand conceptually; the use of vague concepts made the process complicated
- It is not clear what cartilage-like phenotype is described by the authors; MSC can be directed towards cartilage or bone phenotypes directly in vitro, however, when used in vivo, they go through the entire endochondral process including a cartilage-like phenotype
- The use of the growth plate is not a correct parameter for comparison when dealing with post-development fracture healing
- The potential to treat bone large segment defects might encounter various technical and regulatory hurdles

DISCOVERY

Application #	DISC1-10491
Title (as written by the applicant)	Manipulating integrins to dedifferentiate primary endothelial cells
Research Objective (as written by the applicant)	To optimize reprogramming of primary human umbilical endothelial cells by simultaneous activation of integrin αvβ3 and suppression of integrins that may counteract its reprogramming potential.
Impact (as written by the applicant)	Integrin-mediated control of differentiation state will advance our scientific understanding of integrin biology and reveal practical applications for regenerative medicine.
Major Proposed Activities (as written by the applicant)	• Aim 1: How do individual integrins impact HUVEC dedifferentiation? • Aim 2: How do individual ECM components impact HUVEC dedifferentiation? • Aim 3: Create a designer matrix to promote HUVEC dedifferentiation
Statement of Benefit to California (as written by the applicant)	Our goal is to understand how primary somatic cells might be reprogrammed by simply modulating the clustering of specific integrins on the surface of each cell, providing multipotent cells that could be used for a variety of regenerative medicine applications. Our work will also have practical applications to enhance the expansion of dedifferentiated stem cells, providing a new tool for stem cell biology.
Funds Requested	$232,200
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 79

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

Mean	76
Median	79
Standard Deviation	5
Highest	80
Lowest	65
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Will the proposed idea have impact on human stem cell research?	5	7	1
Is the scientific premise valid?	4	5	4
Is the experimental plan adequately designed to test the idea?	2	6	5
Is the proposed project duration appropriate?	5	0	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

- Interesting integrin research
- Excellent team - really well written proposal
- Really strong group

Concerns

- Conceptually difficult to understand how the reprogramming is achieved
- Seems too simple to get reprogramming with integrin signaling
- Limited improvement of reprogramming technology
- HUVEC do not have any clinical application
- Not applicable to fibroblast dedifferentiation; HUVEC are not the right model

DISCOVERY

Application #	DISC1-10560
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 from specific donors, increasing the number of patients we can treat. Our work will also help guide new research in this scientific 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 but a fraction of the number of patients who could benefit from such stem-cell based therapy for several different conditions. If we are successful in our project, we can greatly increase access to this most successful of stem cell treatments to Californians who suffer from a variety of diseases, including cancer and immune disorders.
Funds Requested	$233,406
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 75

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

Mean	75
Median	75
Standard Deviation	5
Highest	85
Lowest	70
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	1
(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
Will the proposed idea have impact on human stem cell research?	3	3	5
Is the scientific premise valid?	6	2	3
Is the experimental plan adequately designed to test the idea?	5	6	0
Is the proposed project duration appropriate?	5	2	4

Reviewer Comments

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

Strengths

- Relevant and strong scientific premise

Concerns

- Did not find the application to be transformational in nature, and did not have the potential for significant impact in moving the field forward
- Proposal not transformational enough to push the field forward
- Flow of logic and figures in proposal are confusing

DISCOVERY

Application #	DISC1-10634
Title (as written by the applicant)	CFIm25 inhibitors as a tool for improving somatic reprogramming efficiency
Research Objective (as written by the applicant)	Test the hypothesis that CFIm25 is a key roadblock gene for human somatic reprogramming and search for small molecules that improve human reprogramming efficiency
Impact (as written by the applicant)	The proposed studies may identify a key roadblock gene for human somatic reprogramming and improve the development of iPSC-based therapeutics and their translation into the clinics.
Major Proposed Activities (as written by the applicant)	• Test the hypothesis that CFIm25 is a roadblock gene for human somatic reprogramming • Perform a chemical screen for CFIm25 inhibitors • Test if CFIm25 inhibitors can improve human somatic reprogramming
Statement of Benefit to California (as written by the applicant)	Patients from California will benefit from improved regenerative medicine that is made possible by our proposed studies.
Funds Requested	$208,544
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 75

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

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

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Will the proposed idea have impact on human stem cell research?	1	2	1
Is the scientific premise valid?	0	1	3
Is the experimental plan adequately designed to test the idea?	0	1	3
Is the proposed project duration appropriate?	0	1	3

Reviewer Comments

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

Strengths

- Strong preliminary data on a new pathway in reprogramming
- Substantial enhancement of mouse reprogramming efficiency through modulation of this pathway is established

Concerns

- Not clear that efficiency of reprogramming is rate limiting for research or therapeutic application of iPSC
- Concept that inhibition would be a good target for small molecule drug development is reasonable but no evidence that it is important for reprogramming
- Preliminary data on human cells would strengthen application and would not be hard to obtain; it is likely that the strategy would work in human cells but a negative result would kill the project
- Experimental plan has an uncertain outcome as the screen is not developed yet, and there is no provision for time for lead optimization
- 12-month timeframe is optimistic

DISCOVERY

Application #	DISC1-10481
Title (as written by the applicant)	Stem cell gene therapy to cure muscular dystrophy
Research Objective (as written by the applicant)	The goal of the proposed studies is to determine whether we can genetically correct muscle stem cells while they are in place in the body by using a simple and safe gene therapy approach.
Impact (as written by the applicant)	If successful, this new strategy could lead to simpler, faster, safer, and more effective ways to correct muscle diseases like muscular dystrophy. through a powerful stem cell approach.
Major Proposed Activities (as written by the applicant)	• Show that we can achieve gene therapy of muscle stem cells in the body after using electroporation of DNA into muscle, using a safe DNA integration system to permanently place the therapeutic genes. • Demonstrate that the corrected muscle stem cells from Activity 1 function in muscle regeneration by transplanting them into other mice and seeing the stem cells form healthy muscle fibers. • Show that the corrected muscle stem cells created in Activity 1 can fully regenerate a healthy muscle after it is damaged with a chemical that destroys muscle fibers. • Determine whether a second gene therapy method involving injecting DNA in blood vessels can correct muscle stem cells in the body, measuring success with the same approaches used in Activities 1 – 3. • Verify that the system we use to integrate DNA into the chromosomes in mice also works in human muscle stem cells by verifying integration after introducing DNA by electroporation. • Show that the human muscle stem cells that we modified will work to create healthy muscle fibers when we transplant them into mouse muscles.
Statement of Benefit to California (as written by the applicant)	This project could benefit California by providing new and effective stem cell therapy approaches for muscle. Thousands of Californian patients with muscle diseases like muscular dystrophy would benefit from better health and more ability to contribute to the economy. Furthermore, if a muscle stem cell treatment center were established in California that attracted patients from across the country and beyond, it would stimulate job formation and economic activity for the state of California
Funds Requested	$235,836
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 75

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

Mean	74
Median	75
Standard Deviation	6
Highest	85
Lowest	65
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	1
(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
Will the proposed idea have impact on human stem cell research?	5	5	4
Is the scientific premise valid?	7	5	2
Is the experimental plan adequately designed to test the idea?	3	6	5
Is the proposed project duration appropriate?	5	1	8

Reviewer Comments

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

Strengths

- The rationale of “in vivo” genetic modification of muscle stem cells is interesting
- Great technology

Concerns

- The proposal brings a series of concerns with regards to potential off-site DNA integration effects, that may create genetic alterations of the targeted cells for which it would be difficult not only to diagnose/identify but also to treat
- The techniques proposed for the gene therapy are not stem cell specific, potentially administering DNA to multiple cell types thus potentially generating undesired secondary effects
- The delivery methods proposed is questioned in terms of its applicability in a clinical setting given the complexity of targeting all muscles in a patient
- Dealing with off-site effects and delivery to patients is a concern

DISCOVERY

Application #	DISC1-10622
Title (as written by the applicant)	Targeted degradation of the retinoblastoma protein for cell reprogramming and tissue regeneration
Research Objective (as written by the applicant)	We will test a novel technology that generates new stem cells.
Impact (as written by the applicant)	We will develop a new therapeutic that safely stimulates tissue repair and wound healing.
Major Proposed Activities (as written by the applicant)	• Develop a new chemical that results in removal of a protein inhibitor to cell division. • Test our new chemical in assays for conversion of ordinary cells into stem cells.
Statement of Benefit to California (as written by the applicant)	Our work will lead to new therapies that improve tissue repair, particularly in patients with severe burns and wounds in need of rapid tissue growth. The pipeline for such therapies is narrow because our current technologies for generating new stem cells are inefficient and our potentially oncogenic. We will develop new molecules that overcome these challenges to stimulate stem cell production without adverse effects.
Funds Requested	$171,700
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 75

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

Mean	74
Median	75
Standard Deviation	10
Highest	84
Lowest	45
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Will the proposed idea have impact on human stem cell research?	2	8	3
Is the scientific premise valid?	3	5	5
Is the experimental plan adequately designed to test the idea?	8	2	3
Is the proposed project duration appropriate?	7	2	4

Reviewer Comments

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

Strengths

- They aim at developing chemical compounds (permeable cyclic peptides) that can increase the efficiency of cell reprogramming
- The use of controlled chemical inactivation could distinguish phenotypes and could be used to understand how tissue-specific tumors develop from these cell population
- This chemical tool could ultimately exploit transient target protein inactivation for increasing the efficiency of reprogramming and the regenerative potential of different cell type
- Important target
- Interesting from standpoint of basic science
- Great system

Concerns

- Application of technology not ideal
- Reprogramming is already quite efficient; new reprogramming methods have reduced impact
- Improving reprogramming is no longer relevant
- Plans for regeneration are not well-planned

DISCOVERY

Application #	DISC1-10612
Title (as written by the applicant)	Immune-compatible universal pluripotent stem cell-derived pancreatic islets graft for the cure of juvenile diabetes
Research Objective (as written by the applicant)	Our overall goal is to engineer a universal stem cell-derived insulin producing cell-graft (SCβ) that will not be rejected by the recipient's immune system, for the treatment of juvenile diabetes.
Impact (as written by the applicant)	If successfully tested, our innovation may allow for SCβ grafts to be an 'off-the-shelf' universal cell product that may cure patients with juvenile diabetes.
Major Proposed Activities (as written by the applicant)	• Induce the expression of the immuno-modulatory molecule PD-l1 on SCβ grafts by genetic editing of the parental pluripotent stem cell line. • Induce blood vessel growth into SCβ grafts and the expression of the immuno-modulatory molecule FasL on the surface of these blood vessel cells.
Statement of Benefit to California (as written by the applicant)	Type 1 Diabetes mellitus is a major cause of morbidity, with 1.25 million American affected. Among U.S. states, California has the greatest number of new cases of diabetes annually. Diabetes costs in California exceed $24 billion each year. Our innovative approach has the potential to overcome the major barrier of immune-compatibility between SCβ grafts and recipient patients. If successfully tested, our innovation may allow for SCβ grafts to be an 'off-the-shelve' universal cell product.
Funds Requested	$235,643
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 70

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

Mean	73
Median	70
Standard Deviation	5
Highest	85
Lowest	65
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	1
(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
Will the proposed idea have impact on human stem cell research?	3	3	5
Is the scientific premise valid?	2	4	6
Is the experimental plan adequately designed to test the idea?	1	7	4
Is the proposed project duration appropriate?	5	1	6

Reviewer Comments

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

Strengths

- Important objective with broad applications
- Interesting strategy

Concerns

- The use of MSCs is not well-justified
- The hypothesis is based on published literature and there are no preliminary data
- Potential for tumorigenesis: Over expression of PD-L1 and Fas-L to promote immune escape is not novel in islet transplantation; promoting uncontrolled immune escape of SC-beta will increase their tumorigenicity
- Proposal is not well-organized; Aim 2 does not fit well with Aim 1
- Unclear plan
- Very ambitious

DISCOVERY

Application #	DISC1-10529
Title (as written by the applicant)	Cochlear delivery of mesenchymal stem cell products for preventing drug-, noise-, and age-related deafness
Research Objective (as written by the applicant)	Determine whether products secreted by adult adipose-derived mesenchymal stem cells can reduce or prevent drug-, noise-, and age-related hearing loss.
Impact (as written by the applicant)	For those persons at risk of deafness, this low-risk administration of stem cell products could enhance normal repair mechanisms and halt the otherwise inevitable progression of hearing loss.
Major Proposed Activities (as written by the applicant)	• Isolate, purify, and characterize products of human adipose-derived mesenchymal stem cells (MSC). • Determine whether delivery of MSC products can prevent or ameliorate ototoxicity.
Statement of Benefit to California (as written by the applicant)	Drug-, noise-, and age-related hearing loss (DRHL, NRHL, and ARHL), together, affect 1 in 3 persons, yet no FDA-approved clinical strategy exists to prevent or treat any of them. The long-term goal of this research is to develop a stem cell-based product that can easily be administered into human ears to halt the progression of hearing loss before it develops to a severe stage. This would reduce costs of healthcare, and would immeasurably improve the quality of life of affected patients.
Funds Requested	$233,999
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 70

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

Mean	66
Median	70
Standard Deviation	13
Highest	80
Lowest	30
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Will the proposed idea have impact on human stem cell research?	3	5	6
Is the scientific premise valid?	2	8	4
Is the experimental plan adequately designed to test the idea?	2	8	4
Is the proposed project duration appropriate?	4	4	6

Reviewer Comments

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

Strengths

- Preclinical study will use human adipose-derived MSC exosomes that have been shown to contain pro-resolution mediators
- Intracochlear delivery of MSC exosomes are a potentially novel therapy for preventing or ameliorating DRHL, NRHL, and ARHL
- Focus on patients receiving ototoxic chemotherapy drugs and patients with significant noise exposure who show early partial hearing loss is a strength
- It is a promising field that may generate therapeutic approaches with potentially less stringent regulatory constraints given the absence of living entities (cells); the "rapid" regulatory clearance would significantly impact patients, should the resulting therapies be safe and efficient
- Novelty and potential for patient benefit

Concerns

- The authors propose that cell-free exosomes may have better therapeutic effects than traditional pharmaceuticals (e.g., steroids) based solely on their known cargo, which is a simplistic assumption
- It is a broad assumption that exosomes fully recapitulate the immunomodulatory and anti-inflammatory capacities of the parent MSC, requiring that the molecules produced by MSC get collectively packaged into the derived exosomes (not necessarily the case)
- The data supporting a benefit of cell-based therapy is not convincing
- Reproducibility and properties of the exosomes are not well addressed and the laboratory has no expertise with exosome biology
- A second time window of injection (post damage) could have increased the scope and relevance
- The medium (and volumes) in which the exosomes will be resuspended (i.e. culture media or saline), are neither described nor suggested; these are two critical factors given the type and site for the therapy proposed
- There is a question of feasibility as the bulk of the work seems to be carried out by one key person who is budgeted for 10%, yet they will perform, coordinate, and supervise study design, supervise exosome molecular analysis, perform animal surgeries and hearing quantification, and analyze resulting data
- There are concerns about lack of expertise in exosomes
- Group did not demonstrate a clear understanding of the variable causes of deafness

DISCOVERY

Application #	DISC1-10615
Title (as written by the applicant)	Hiring bodyguards on the trip: Interaction between metastatic cancer stem cells and T regulatory cells
Research Objective (as written by the applicant)	The objective of this research is to study mechanisms how tumor stem cells evade immunotherapies with emphasis on identification of cellular interaction between metastatic tumor stem cells and Tregs.
Impact (as written by the applicant)	If successfully realized, our proposed work will unveil new information that leads to the development of targeted approaches, or in combination with current immunotherapies to reduce metastasis.
Major Proposed Activities (as written by the applicant)	• Identification cellular interaction between human metastatic tumor stem cells and Tregs in a humanized model. • In vivo examination of chemokine production by human metastatic stem cell.
Statement of Benefit to California (as written by the applicant)	Recurring tumor and metastasis are the major causes of deaths and affect millions of Californians. No effective treatments currently exist, in part because we know very little about the regulation in cancer stem cells. Our proposed study will identify new mechanism how human tumor stem cells escape immunotherapy and will lead to discovery of new treatments. An effective therapy will reduce healthcare cost burden to taxpayers. Healthy population can also contribute to increase State tax revenues.
Funds Requested	$180,000
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 65

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

Mean	66
Median	65
Standard Deviation	7
Highest	85
Lowest	60
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	1
(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
Will the proposed idea have impact on human stem cell research?	5	3	4
Is the scientific premise valid?	3	5	4
Is the experimental plan adequately designed to test the idea?	1	7	4
Is the proposed project duration appropriate?	3	2	7

Reviewer Comments

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

Strengths

- The notion of interactions between cancer stem cells and Treg cells is innovative and potentially impactful on cancer immunotherapy
- Very novel
- The overall hypothesis is very exciting
- It would be interesting to explore where CSCs and Tregs interact

Concerns

- A more tightly focused hypothesis would be appropriate for a small project; it would be better to investigate either of the aims more deeply
- A more specific hypothesis specifying proposed molecular mediators of this complex is needed; typically, cells that communicate only by soluble mediators would not be called "a complex"
- Characterization of the "complex" is not clear
- The proposal lacks important controls to validate experimental results
- Controls and experimental details are missing
- A positive control and null reagents to demonstrate non-specific pulldown is not a problem are needed
- Expected results are not discussed and translation to the clinic is not laid out
- Very risky - not enough details

DISCOVERY

Application #	DISC1-10493
Title (as written by the applicant)	Self-renewal and differentiation defects hypothesized to arise in disease
Research Objective (as written by the applicant)	We will test the hypothesis that mutations responsible for genetic disease may also alter stem-cell differentiation, which has implications for both understanding the disease and how to treat it.
Impact (as written by the applicant)	The potential impact is the uncovering of an important variable that influences stem cell differentiation that would be relevant to stem cell therapies involving patients with these diseases.
Major Proposed Activities (as written by the applicant)	• Generate and characterize a panel of isogenic iPSC cell lines that differ only in the presence (or absence) of a mutation linked to a genetic disease that disrupts development. • Evaluate the hypothesized differences in signal intensity within the isogenic panel of mutant iPSC. • Evaluate whether the mutations associated with disease alter the requirements for pluripotency maintenance factors. • Evaluate whether the mutations associated with disease disrupt stem cell differentiation kinetics. • Evaluate whether the mutations associated with disease can cause differentiation into different lineages than non-mutant, isogenic, iPSC.
Statement of Benefit to California (as written by the applicant)	This research aims to investigate an important variable that we hypothesize plays an important role in how stem-cells develop into new cell types. A better understanding of this process could facilitate stem-cell based therapies. We are particularly interested in genetic diseases that may influence stem-cell biology. This could benefit citizens who have one of these diseases.
Funds Requested	$284,580
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 65

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

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

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Will the proposed idea have impact on human stem cell research?	0	2	2
Is the scientific premise valid?	0	2	2
Is the experimental plan adequately designed to test the idea?	0	2	2

Is the proposed project duration appropriate?	0	0	4

Reviewer Comments

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

Strengths

- The important role of the variability of signaling "strength" or "noise" in in vitro cell systems is well known and is thus likely to also affect in vitro cultured stem cells. The applicant proposes that different mutations will lead to a different spectrum of signaling "noise" in stem cell systems that could alter their differentiation profile which seems reasonable.
- A premise that motivates this proposal is that human iPSC cells are different than mouse cells and that human mutant cell lines have been less studied. While this is certainly true and more research is warranted, a strong role for the "noise" angle is not apparent.
- The applicant will generate a number of isogenic human cell lines that might be useful.
- The establishment of isogenic human iPSC with a pathogenic mutation is a valuable contribution to the field.

Concerns

- A novel aspect of the application is the suggestion that increasing "uniformity" of signalling (rather than just reduction of output) will be disease altering and therefore a novel therapeutic target. While interesting, this hypothesis is, however, not directly addressed in the experiments.
- The only readout is proliferation, which we know already from animal models is affected. It would have been helpful if the applicant would have provided insight into how the ideas of "noise" in signaling can be incorporated into a more effective drug screen or can provide a novel therapeutic approach. Such a section is missing.
- The analysis remains quite superficial and time, medium pH, O2 levels and cell density might all affect the cultures independently of the growth factor levels. It is not clear how the applicant controls all the other potential in vitro culture aspects that can influence rates of proliferation.

DISCOVERY

Application #	DISC1-10581
Title (as written by the applicant)	Reprogramming of human pancreatic exocrine cells into beta-like endocrine cells
Research Objective (as written by the applicant)	Reprogram human exocrine cells that were left over from islet transplantation into functional endocrine-like cells that can be used clinically to treat type I diabetes.
Impact (as written by the applicant)	The procedure may provide massive amount of endocrine like cells that can be used for islet transplantation, and also explore the advantage of partial versus compete in somatic cell reprogramming.
Major Proposed Activities (as written by the applicant)	• Develop procedure to culture human exocrine cells for a substantial longer time and maintain their exocrine cell characteristics to facilitate partial reprogramming procedure. • Partial reprogram human exocrine cells left over from islet isolation to pancreatic progenitor cells or endocrine precursor cells by OSKM factors (OCT4, SOX2, KLF4, and MYC) using protein transfection or CRISPRa approaches. • Treats OSKM dedifferentiate cells with PDX1, NGN3, and MAFA using protein transfection or CRISPRa mediate gene activation. • Manipulating PAX4 (protein transfection or CRISPRa), ARX, and HHEX (CRISPRi or RNAI) to direct the dedifferentiation of pancreatic progenitor cells or endocrine precursor cells into beta cells. • Beta-like cell characterization. Q-PCR and antibody stain will be used to detect beta, alpha, and delta specific gene expression. Insulin, SST, GCG, will be checked. • Compare reprogrammed beta cells with EndoC-BH1 cell line for glucose response, insulin production level, and possible gene expression profile, miRNA profile.
Statement of Benefit to California (as written by the applicant)	Diabetic patients are increasing at an alarm rate. Islet transplantation is an effective therapy for type 1 diabetes. But it suffers from a bottleneck problem: the shortage of pancreas donors. On the other hands, the majority of exocrine cells in pancreas are not used for islet transplantation. The proposed procedure will convert left over exocrine cells from islet transplantation to functional endocrine cells. It will be a key medical resource for the State of California and its citizens.
Funds Requested	$231,248
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 65

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

Mean	58
Median	65
Standard Deviation	16
Highest	80
Lowest	10
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Will the proposed idea have impact on human stem cell research?	6	6	0
Is the scientific premise valid?	2	9	1
Is the experimental plan adequately designed to test the idea?	3	9	0
Is the proposed project duration appropriate?	4	3	5

Reviewer Comments

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

Strengths

- Very impactful: Current reprogramming protocols do not regenerate functional beta cells; improving those protocols will allow producing sufficient numbers of beta cell for replacement therapies through transplantation for type-1 diabetes
- Clear rationale: they propose to reprogram exocrine cells transiently into pancreatic progenitor cells and then re-differentiate them into beta cells

Concerns

- The idea and approach of the proposal to reprogram pancreatic exocrine cells into beta cells is not novel
- They claim that their protocol will generate more functional beta cells but there are no data to support this hypothesis
- Doubts about feasibility of the approach

DISCOVERY

Application #	DISC1-10550
Title (as written by the applicant)	Directed Epigenetic Reprogramming for Cardiac Regeneration
Research Objective (as written by the applicant)	Directed reprogramming of cardiac fibroblasts using novel technology for cardiac regeneration
Impact (as written by the applicant)	The proposed therapy would offer highly attractive option for the treatment of patients with heart failure, which affects approximately 5.7 million people in the U.S.
Major Proposed Activities (as written by the applicant)	• Identifying cardiac specific factors for reprogramming • Examining the induction of cardiac gene expression • Assessing the functional characteristics of reprogrammed cardiac cells • Understanding the mechanisms involved in reprogramming process
Statement of Benefit to California (as written by the applicant)	Cardiovascular disease remains the leading cause of death and causes more deaths than all cancers combined. The loss of cardiac cells due to heart attack can result in heart failure. Since cardiac cells can not sufficiently replace the damaged heart, we need to explore the use of other cells for cardiac regeneration. Our research aims at converting the abundantly available non-cardiac cells within the heart into functional cardiac cells using novel technology to facilitate cardiac regeneration.
Funds Requested	$235,800
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 62

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

Mean	59
Median	62
Standard Deviation	13
Highest	70
Lowest	30
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Will the proposed idea have impact on human stem cell research?	5	4	3
Is the scientific premise valid?	4	5	3
Is the experimental plan adequately designed to test the idea?	2	6	4
Is the proposed project duration appropriate?	4	1	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

- Targeting endogenous transcription factors is likely to be an effective approach for reprogramming fibroblasts to cardiomyocytes

Concerns

- The project seems to be an incremental advance as the advantages of targeting endogenous transcription factors vs. exogenous expression is not evident
- The claims of mechanistic insight into reprogramming are not well-supported

DISCOVERY

Application #	DISC1-10716
Title (as written by the applicant)	Novel Acousto-Microfluidic Platform for Detecting Endothelial Progenitor Cells
Research Objective (as written by the applicant)	Demonstrate feasibility of chip based clinical technologies for accurate enumeration of endothelial progenitor cells from biological samples
Impact (as written by the applicant)	This portable, low-coast and easy-to-operate platform will help making critical decisions at clinical settings and help early detection of heart diseases
Major Proposed Activities (as written by the applicant)	• Develop an efficient surface functionalization scheme for specific capturing of endothelial progenitor cells on microfluidic channels walls • Develop a in-channel fluorescence cell membrane labeling method to efficiently enumerate the endothelial progenitor cells captured on channel walls. • Optimize device operation parameters for high efficiency (90%) capturing of endothelial progenitor cells controllably spiked in serum samples • Optimize operation parameters for high efficiency capturing of spiked endothelial progenitor cells in serum solutions with background leukocyte cells, similar to buffy coat obtained from blood samples • Demonstrate high-efficiency (90%) isolation of endothelial progenitor cells in similar conditions to Activity-4 within an hour.
Statement of Benefit to California (as written by the applicant)	Cardiovascular diseases account for one third of the all deaths in California as of year 2014. That is loss of approximately 80,000 Californians within in a year. The economic burden of cardiovascular diseases on the state is close to 37 billion dollars as of 2010. The low-cost clinical tool proposed here to monitor endothelial progenitor cells for early diagnostics of cardiovascular diseases could help making critical decisions on time, saving lives and bringing health care costs down.
Funds Requested	$172,277
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: --

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

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

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Will the proposed idea have impact on human stem cell research?	3	7	2
Is the scientific premise valid?	3	5	4
Is the experimental plan adequately designed to test the idea?	4	4	4
Is the proposed project duration appropriate?	5	1	6

Reviewer Comments

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

Strengths

- Innovative concept that could expand the range of clinical diagnostic axes
- Many other applications could be envisioned
- The use of acoustic forces is likely to enhance cell-substrate interactions, enabling more efficient cell isolation in a microfluidic device
- It would be useful to have an efficient diagnostic technique using circulating stem cells
- Feasible plan

Concerns

- Incremental rather than transformative
- Endothelial progenitors cannot be isolated using single surface markers; multiplexing is not addressed
- There is a lack of evaluation of the cells isolated in the device
- A description of the statistics and how positive and negative controls will be used is needed; for example, "Successful completion of this activity will result in more than 90% efficient isolation of EPCs from buffy coat like sample solutions with 1:10000 leukocyte ratios within an hour."
    - Determine how they will know that they have achieved this milestone
    - Define the statistical test to be used, power, and 'N' needed

DISCOVERY

Application #	DISC1-10506
Title (as written by the applicant)	Magnetic Nanoparticles as Mesenchymal Stem Cell Trackers
Research Objective (as written by the applicant)	To use MRI for in vitro viewing of MNP labeled-mesenchymal stem cells.
Impact (as written by the applicant)	Delivery and concentration of stem cells in targeted tissue can improve.
Major Proposed Activities (as written by the applicant)	• Synthesis of biocompatible magnetic nanoparticles (MNPs) • Conjugation of the MNPs to MSCs • Analysis of MNPS and conjugates: stability in physiological media, magnetic properties, cell viability assay • Analysis of MSCs: cell viability assay and light microscopy • Imaging, characterization, and optimization of MNP-MSCs in vitro • Reiterations: resynthesize MNPs if any of the above activities yield unsatisfactory results
Statement of Benefit to California (as written by the applicant)	Stem cell implants are regularly used after leukemia chemotherapy, and stem cells have the potential to treat many ailments involving tissue damage or death. With proper imaging techniques , it is possible to better understand what is necessary to ensure they arrive at damaged tissue and participate in its recovery.
Funds Requested	$102,582
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: --

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

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

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Will the proposed idea have impact on human stem cell research?	1	3	1
Is the scientific premise valid?	0	1	4
Is the experimental plan adequately designed to test the idea?	1	3	1
Is the proposed project duration appropriate?	1	2	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 project addresses a key limitation in the translation of stem cell therapy development, the lack of the ability for long-term tracking of cells in vivo
- The central idea is interesting and of great impact for the field of stem cell research
- The proposal would have a great impact on stem cell research for tracking cells after administration and would help answer several questions related with biodistribution of the cells including location and timing information
- Tracking MSC distribution after delivery and interaction with T cells will increase safety of therapy and help understand mechanisms of action

Concerns

- Although the scientific premise is valid (to track MSC after administration), the authors failed at providing a comprehensive rationale to support the project
- MRI applications are not proposed and these will be crucial to testing the idea
- Biocompatibility is not the limiting factor in magnetic nanoparticle imaging; signal sensitivity and dilution is more pressing at this point
- Experimental plan lacks details
- The experiments are not presented in enough detail; for instance, when proposing to analyze the MNP uptake by MSC, the authors wrote: “There are several staining techniques that stain cells containing MNP atoms”
- The text is difficult to understand and lacks supportive evidence and hypothesis structure (especially when talking about stem cells)
- Very ambitious for the timeline proposed

DISCOVERY

Application #	DISC1-10468
Title (as written by the applicant)	Age-related Reduction of Human Muscle-specific Stem Cells Limits Functional Recovery after Rotator Cuff Injury
Research Objective (as written by the applicant)	Determining the prevalence of human muscle-specific stem cells and their potential for phenotypic conversion down the fibroblast lineage
Impact (as written by the applicant)	This work has the potential to directly change the management of rotator cuff injuries by exploiting the possibility of modulating stem cell niche signals
Major Proposed Activities (as written by the applicant)	• Determine the prevalence of Muscle Specific-Stem Cells in Human Rotator Cuff Muscles after musculoskeletal injury relative to non-injured muscle • Determine the prevalence of Muscle Specific-Stem Cells in Human Rotator Cuff Muscles after neurological injury relative to non-injured muscle • Determine the Ability of Human Muscle Specific-Stem Cells for niche remodeling and modulation so as to restore their myogenic potential with a xenotransplantation model
Statement of Benefit to California (as written by the applicant)	Rotator cuff (RTC) injuries affect 30% of the 60+ population and often leave patients with irreversible functional deficits even with surgery due to muscle degeneration and fibrosis. This research will provide direct answers about altering the path of degeneration of the RTC into fibrotic tissue. By doing so, we can restore functional mobility for this active population, reduce the number of CA citizens that will need a shoulder replacement, and thereby decrease CA healthcare costs.
Funds Requested	$230,502
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: --

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

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

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Will the proposed idea have impact on human stem cell research?	1	3	2
Is the scientific premise valid?	1	3	2
Is the experimental plan adequately designed to test the idea?	1	4	1
Is the proposed project duration appropriate?	3	2	1

Reviewer Comments

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

Strengths

- The idea of stem cell niche modulation in muscle is new

Concerns

- There are several ideas and concepts merged, making it difficult to discern what is the real central hypothesis and how the potential outcomes could be transformed into therapies
- The proposal is centered around the potential reduction in numbers of muscle stem cells in aged patients with rotator cuff injury, but it is very difficult to see the translation of this into a therapy
- The authors describe the modulation of the stem cell niche as novel approach, but it is not clear that the proposal will address that experimentally

DISCOVERY

Application #	DISC1-10673
Title (as written by the applicant)	Major Histocompatibility Complex (MHC) Class I expression during spontaneous differentiation of iPSCs.
Research Objective (as written by the applicant)	The objective is to characterize Major Histocompatibility Complex (MHC) expression as iPSCs spontaneously differentiate down the three different germ layers.
Impact (as written by the applicant)	Knowledge of MHC expression, will help us time interventions with cellular therapies and create less immunogenic cells, which may be more viable for transplantation.
Major Proposed Activities (as written by the applicant)	• We will obtain iPSCs from at 10 different disease-free donors from the iPSCORE bank housed at the WiCell Research Institute or ATCC. • To begin differentiation, we will grow up the iPSC lines in DMEM/F12 medium in a feeder free environment to form Embryoid Bodies (EBs). • We will grow EBs for up to 7 days to allow them to spontaneous differentiate for 8-20 days. • After the cells begin to migrate away, they begin to differentiate into the three germ layers. We will take a sample of the cells and stain them for the three different germ layer markers. • We will also take a sample of these cells and to stain for the presence of MHC expression and use Flowcytometry to quantify the cells expressing MHC. • We will prepare a manuscript for publication on the findings.
Statement of Benefit to California (as written by the applicant)	The proposed research will provide basic knowledge on processes related to stem cell therapeutics and transplantation. This will further research and treatment for diseases that will be treated and/or cured with stem cells. This will benefit the State of California and its citizens through the scientific progress and support for stem cell treatments and cures.
Funds Requested	$180,000
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: --

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

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

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Will the proposed idea have impact on human stem cell research?	0	2	2
Is the scientific premise valid?	0	2	2
Is the experimental plan adequately designed to test the idea?	0	3	1
Is the proposed project duration appropriate?	0	2	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

- Generation of data on MHC Class I expression in stem cells is valuable data

Concerns

- Already fairly well established that MHC expression is low in hPSC and increases on differentiation
- It is unclear exactly what the path to translation from this project would be
- Not clear how results will lead to improvement in hPSC based therapy, and other approaches to modulation of immunogenicity of hPSC derived cells are under investigation
- EB differentiation not relevant to cell therapy; specific differentiated cell products should be tested
- Rather than a general survey of iPSCORE, tying the survey of MHC Class I expression to a specific problem or bottleneck currently recognized in a specific disease or condition may be more useful
- No functional test of immunogenicity of differentiated cells or stem cells is included in the experimental plan
- Achievements during timeframe will provide incremental advance at best
- Apparent lack of recent grants and research output in the biosketch - perhaps project would be stronger if paired with a co-PI with more recent documented experience
- Finding a mentor with experience writing CIRM grants, and working with them to craft an idea and forge it into a strong proposal is recommended