TOTAL BUDGET: TRAN 2016, CYCLE 2

TIER 1 $16,563,513

TIER 2 $44,592,417

App #	Title	Score	Mean	SD	Low	High	Budget	Tier	T1	T2
TRAN1-09394	Human iPSC-derived GABAergic Progenitors for Alzheimer's Disease Treatment	90	89	2	85	90	$5,944,681	1	14	0
TRAN1-09292	Curing Sickle cell Disease with CRISPR-Cas9 genome editing	85	87	2	85	90	$4,463,435	1	13	0
TRAN1-09288	Pluripotent stem cell-derived chondrocytes for articular cartilage repair	85	86	4	80	90	$2,503,104	1	11	3
TRAN1-09270	An autologous somatic stem cell therapy for the treatment of osteonecrosis	86	84	6	70	90	$3,652,293	1	7	5
TRAN1-09293	Injectable pro-regenerative scaffold for treating symptomatic peripheral artery disease	75	79	4	75	88	$2,607,985	2	3	12
TRAN1-09326	Human embryonic stem cell-derived natural killer cells for cancer treatment	75	78	5	70	85	$4,518,815	2	3	10
TRAN1-09286	Extracellular Vesicles (EVs) from Allogeneic Cardiosphere-Derived Cells (CDCs) to Treat Stroke	80	78	3	75	80	$4,820,179	2	0	15
TRAN1-09353	Stem Cell gene therapy to restore blood flow in critical limb ischemia	80	76	12	50	85	$2,577,936	2	3	10
TRAN4-09420	Sample pre-enrichment integrated with FACS to improve high purity cell isolation for the discovery and development of stem cell based therapies	70	73	7	60	90	$1,286,185	2	1	12
TRAN1-09313	Lentiviral Gene Therapy for Bone Repair with Transduced Adipose Derived Stem Cells	70	72	4	70	85	$3,063,457	2	1	13
TRAN1-09317	Tissue Engineered Tracheal Regeneration and Repair	70	70	8	50	85	$5,255,860	2	1	14
TRAN1-09310	hESC-derived retina organoids for vision repair in degenerative retina diseases.	70	68	9	50	80	$4,800,901	2	0	14
TRAN1-09263	Autologous iPSC-derived smooth muscle cell therapy for urinary incontinence	70	66	10	40	80	$6,078,186	2	0	14
TRAN1-09365	Development of an Effective Mobilizer of Stem Cells	68	66	6	60	80	$2,945,300	2	0	14
TRAN3-09311	Novel Device for Stem Cell Delivery into Brain Tumors	--	--	--	--	--	$2,193,342	2	0	13
TRAN1-09305	Novel combination therapy of repurposed FDA-approved drugs targeting liver cancer stem cells	--	--	--	--	--	$1,485,851	2	0	13
TRAN1-09322	Cellular therapy designed to delay Huntington's disease progression	--	--	--	--	--	$2,958,420	2	0	13

Application #	TRAN1-09263
Title (as written by the applicant)	Autologous iPSC-derived smooth muscle cell therapy for urinary incontinence
Translational Candidate (as written by the applicant)	Patient (autologous) iPSC-derived smooth muscle cell progenitors to regenerate and restore function to the deficient urethral sphincter muscle
Area of Impact (as written by the applicant)	Urinary incontinence due to a deficient urethral sphincter muscle
Mechanism of Action (as written by the applicant)	The autologous iPSC-derived smooth muscle cell progenitors (pSMC) are injected into the urethral sphincter muscle to restore and regenerate the smooth muscle component of the urethra. The smooth muscle provides continuous, non-voluntary closure of the bladder during daily activities. Thus, it is critical for continence. Our target therapy works by inducing the native tissue to produce elastin and by integration of the injected pSMCs. This combination results in a functional urethral sphincter.
Unmet Medical Need (as written by the applicant)	Current treatments include injection of materials to "bulk up" the muscles or surgical implantation of meshes. Injections provide only partial and temporary relief. Surgical implants can cause urinary retention and the debilitating "mesh complications". Thus, there is great need for new therapies.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Development of cGMP compliant procedures for isolation and production of patient specific iPSC banks, and production of pSMC • Creation of 3 pSMC pre-clinical qualification lots from iPSC banks to supply the proposed safety trials • Development of pre-clinical GLP toxicology/tumorigenicity and efficacy studies to be included in the pre-IND package
Statement of Benefit to California (as written by the applicant)	Urinary incontinence (UI) is common and serious, with two-thirds of the burden borne by women. UI impacts quality and length of life; women with UI suffer debilitating falls, experience social isolation, and are more likely to be depressed. Many Californians with UI are not relieved by current treatments. The target therapy will restore function to a deficient urethral muscle. This product should enhance safety relative to many current options, and reduce cost by avoiding surgery.
Funds Requested	$6,078,186
GWG Recommendation	***Not recommended for funding***

Scoring Data

Final Score: 70

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

Mean	66
Median	70
Standard Deviation	10
Highest	80
Lowest	40
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (1-84): Not recommended for funding	14

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	9	3	2
Is the rationale sound?	0	8	6
Is the proposal well planned and designed?	1	7	6
Is the proposal feasible?	0	6	8

Reviewer Comments

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

Strengths

- Well prepared proposal.

Concerns

- Perhaps pre-mature for translation. Is this better than other existing cellular therapies for incontinence? Conversion of fibroblasts into muscle cells through re-programming and differentiation seems time-consuming and complex. Purity and efficacy of cells is not convincing. There are safety concerns , .i.e, potential for teratoma formation.
- Lack of understanding of how the implants would work.
- Need to be convinced autologous iPS is superior to alternative stem cell sources.
- Would need much stronger evidence that this is a uniquely efficacious approach to justify the high cost and complexity of the iPS cell approach- including a difficult differentiation process and complex isolation procedure for the smooth muscle cells of interest.
- Lengthy primary cell isolation, reprogram, expansion process. Final product purity may be called into question.
- One challenge to consider is the complexity of the production process and whether it is better than other more simple procedures.
- Additional data demonstrating patient to patient variability for both reprogramming and differentiation processes is critical. There is also room for improvement on the process side (e.g.,use of Matrigel); the requirement for both FACS and CliniMACs negative selections.
- Efficacy data is not adequate. Data beyond upregulation of elastin and other ECM proteins was not provided. LPP data was not presented and should be compared to other potential treatment options if possible.
- Limited efficacy in a rodent model is concerning.
- Risk of teratomas remains significant.
- Safety of the cell implants is a concern as it is not known how many PSC's are present in the injected material.
- The residual undifferentiated cell assay is critical for the safety of the product. The assay should be qualified and LOD be established for this critical assay. The plans for qualifying this assay should be detailed in the proposal leading up to the tumorigenicity study and pre-IND.
- The group should be encouraged to resubmit once they have addressed these issues and compared risk-benefit and complexity/cost to Cook Myosite. Is the failure rate of muscle biopsy expansion higher than the failure rate of iPSC derivation and pSMC differentiation?

Application #	TRAN1-09270
Title (as written by the applicant)	An autologous somatic stem cell therapy for the treatment of osteonecrosis
Translational Candidate (as written by the applicant)	An autologous somatic stem cell therapy for the treatment of osteonecrosis.
Area of Impact (as written by the applicant)	Osteonecrosis is a painful, progressive disease for which there is no treatment, save replacing the dead bone with a metal implant.
Mechanism of Action (as written by the applicant)	Autografts contain skeletal stem cells. In young patients, these stem cells differentiate and give rise to new bone but in older patients, autografts are ineffective. The WNT therapeutic ART352-L re-activates stem cells in an older person's autograft and the resulting material, ART1001, generates more osteo-progenitor cells and engrafts better than untreated autografts. In preclinical models ART1001 outperforms the standard of care and leads to superior healing of osteonecrotic lesions.
Unmet Medical Need (as written by the applicant)	Osteonecrosis is a disease that "causes jawbones to rot and thighbones to snap", and its incidence is on the rise in our aging population. The autologous somatic stem cell therapy ART1001 has the potential to generate more bone, sooner in these older patients with osteonecrotic lesions.
Project Objective (as written by the applicant)	Conduct of a well prepared pre-IND meeting.
Major Proposed Activities (as written by the applicant)	• ART352 process development; development of liposomal formulation (e.g., ART352-L); GLP production of ART352 and ART352-L; stability studies. • Evaluate safety of the autologous stem cell product ART1001; validate method of ART1001 delivery in a large animal model • Determine clinical plan and regulatory pathway for ART1001; schedule and conduct a pre-IND meeting with the FDA.
Statement of Benefit to California (as written by the applicant)	For Californians over 45, low bone mass diseases are a major public health threat: They account for more days spent in hospital than diabetes and heart attacks, and their related disabilities are greater than those caused by cancers. ART1001 has the potential to dramatically improve bone healing in this older population. Such an improvement in the SOC will result in better outcomes, fewer complications, and a quicker return of older individuals back to the activities of daily living.
Funds Requested	$3,652,293
GWG Recommendation	***Recommended for funding***

Scoring Data

Final Score: 86

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

Mean	84
Median	86
Standard Deviation	6
Highest	90

Lowest	70
Count	12
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	7
Tier 2 (1-84): Not recommended for funding	5

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	11	0	1
Is the rationale sound?	10	0	2
Is the proposal well planned and designed?	8	2	2
Is the proposal feasible?	6	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

- Simple product concept with strong rationale to address an important unmet need.
- The procedure to “activate” the autograft into ART1001 is simple, reliable and short. It can be performed by the surgeon during the surgical procedure as it is neither time-consuming nor complex.
- This project is based on pre-clinical evidence (MOA, safety and efficacy) showing the superiority of ART1001 compared with untreated bone autografts treating bone defect and osteonecrosis (lead indication).
- Very strong proposal and well constructed development plan.
- This is a simple but highly innovative approach modulating the WNT pathway in bone marrow while avoiding systemic modulation of WNT.

Concerns

- Uncertainty about regulatory path - feasibility concern.
- The statements are based on the premise that the osteogenic potential comes “exclusively” from the autograft’s resident stem cells differentiating into secretory osteoblasts. However, there was no mention about potential activity on already differentiated local osteoblasts and their secretory capacity. This may have an impact on the designation by the FDA.
- The application lacks supporting data that are found in earlier publications.
- Need more evidence for activity of Wnt3A on human material.
- Unclear if treatment will really impact efficacy over autograft alone.
- Lots of cartoons rather than data to support this technology.
- Strong concern that the "enhanced bone" is not as thick or strong as it may need to be as a reasonable solution- this concern may have been avoided with the inclusion of supporting data.

Additional Comments

- Seems likely this will be a combination device.
- Recommendations to the team: Prepare a backup plan in case the product is designated as a combination product.

Application #	TRAN1-09286
Title (as written by the applicant)	Extracellular Vesicles (EVs) from Allogeneic Cardiosphere-Derived Cells (CDCs) to Treat Stroke
Translational Candidate (as written by the applicant)	Extracellular Vesicles (EVs) from Allogeneic Cardiosphere-Derived Cells (CDCs)
Area of Impact (as written by the applicant)	A novel method to treat stroke to be used in combination with reperfusion therapy, thrombolysis and/or endovascular procedures.
Mechanism of Action (as written by the applicant)	This program offers a realistic adjuvant therapeutic option for stroke victims. We will advance CDC-exosomes to an IND level for testing in a select population of stroke patients receiving current standard of care rt-PA therapy. Exosomes are an excellent therapeutic option for stroke because they have previously been shown to have anti-inflammatory properties, reduce apoptosis and offer the possibility of regenerative process induced by growth factors or the recruitment of endogenous stem cells.
Unmet Medical Need (as written by the applicant)	Stroke is currently treated using thrombolysis with recombinant tissue plasminogen activator (rt-PA or tPA) or endovascular procedures. However, only 13.5-31% of patients undergoing the procedures end up "normal" neurologically after reperfusion therapy. There is a need to a neuroprotective therapy.
Project Objective (as written by the applicant)	We will file a pre-IND application.
Major Proposed Activities (as written by the applicant)	• Evaluate CDC-exosome bioactivity in the rabbit embolic stroke model (Lapchak) alone and in combination with standard-of-care therapy, tPA (Lapchak) • Establish CDC-exosome bioactivity in aged rodents and conduct gender analysis (Lyden) • Evaluate CDC-exosome bioactivity and safety in a large animal stroke model: mRI and behavioral analysis (Cook).
Statement of Benefit to California (as written by the applicant)	Reperfusion therapies have been shown to be effective in up to 31% of patients who become clinically normal following either monotherapy of combined therapy. Neither thrombolysis nor endovascular procedures promote neuroprotection to prevent brain cell death associated with ischemic insults, nor do they promote brain neuroplasticity or regeneration. With CDC-exosomes to treat ischemic stroke, we have the opportunity to have a tremendous impact on a large stroke patient population in California.
Funds Requested	$4,820,179
GWG Recommendation	***Not recommended for funding***

Scoring Data

Final Score: 80

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

Mean	78
Median	80
Standard Deviation	3
Highest	80
Lowest	75
Count	15
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (1-84): Not recommended for funding	15

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	11	2	2
Is the rationale sound?	4	7	4
Is the proposal well planned and designed?	5	4	6
Is the proposal feasible?	10	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

- None noted.

Concerns

- Concerns about regulatory approach, definition of the mechanism of action and definition of the GMP parameters.
- There is critical information that would be needed for greater enthusiasm. There is only poor characterization of the proposed product and of its effects. Applicant appears to overstate data (e.g., the statement that exosomes are somehow targeting the penumbra is not well supported).
- The data shown in Figure 4 shows that proposed product has no effect whatsoever on survival even in this highly controlled laboratory environment.
- One of the critical limitations of TPA therapy is that it is limited to a brief post-stroke window. No experiments were conducted to see if the window of treatment opportunity could be expanded with the proposed product. Applicant proposes to do this, but considering the enormous number of failures in the stroke field, this would be information that would be helpful to obtain early on.
- If it is thought that cells exert benefits by exosome release, then why would a single administration of exosomes be better than administration of cells that would be a continuous source of exosomes? Thus, the product rationale is not clear.
- The proposed single dose administration is not likely adequate (multiple doses are quite likely) unless the applicant can demonstrate longer-term therapeutic value.
- Data evaluating earlier time points would be helpful.
- Mode of action is unclear. Concern that exosome product is insufficiently characterized. What is responsible for biological activity?
- The exosomes are not well defined from a dosing perspective. Is dosing based on mass/volume of total protein? However, the active components are critical and there are likely many non-active or even potentially negative components.
- The study in the rabbit model looking at survival did not demonstrate a significant impact of exosomes relative to the vehicle control.
- No potency assay.
- Efficacy not sufficiently documented.
- Could benefit from early discussions with FDA as a PPIND especially since there are not other INDs using exosomes for therapy derived from cellular products.

Application #	TRAN1-09288
Title (as written by the applicant)	Pluripotent stem cell-derived chondrocytes for articular cartilage repair
Translational Candidate (as written by the applicant)	We propose to develop a universal, off-the-shelf treatment for articular cartilage repair based on pluripotent stem cell (PSC)-derived chondrospheres
Area of Impact (as written by the applicant)	The proposed therapy could treat the major cartilage lesions present in more than 10% of people under 50; which often result in pain and arthritis
Mechanism of Action (as written by the applicant)	Untreated cartilage defects often lead to joint pain and degeneration over time, often requiring joint replacement. The proposed candidate is a universal cell therapy designed to generate new articular cartilage in these defects and interrupt the cycle of degeneration.
Unmet Medical Need (as written by the applicant)	Approximately 10% of people under 50 have at least a single, high-grade defect in their knee cartilage; these lesions have a high probability of promoting subsequent degenerative processes, often resulting in arthritis. Currently, there are no effective treatments for altering this progression.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Optimization of large-scale production, preservation and quality control of pluripotent stem cell-derived chondrocytes • Conduct nonclinical safety and stability tests in small and large animal models • Develop a draft clinical protocol and synopsis and conduct a successful pre-IND meeting
Statement of Benefit to California (as written by the applicant)	The work described in this proposal is designed to produce a universal treatment for articular cartilage lesions. If successfully validated, this cellular therapy will likely help reduce joint pain and reduce further degeneration of joints that leads to arthritis. The proposed treatment may be of major public benefit, as it would represent the first curative strategy for cartilage injury and subsequent degeneration, likely decreasing economic burden on the state and its people.
Funds Requested	$2,516,646
GWG Recommendation	***Recommended for funding***

Scoring Data

Final Score: 85

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

Mean	86
Median	85
Standard Deviation	4
Highest	90
Lowest	80
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	11
Tier 2 (1-84): Not recommended for funding	3

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	14	0	0
Is the rationale sound?	12	0	2
Is the proposal well planned and designed?	10	0	4
Is the proposal feasible?	10	1	3

Reviewer Comments

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

Strengths

- An important approach, with significant need for an intractable condition.
- Strength in the research group with known track record.
- Proactive regulatory interaction.
- The off-the-shelf nature of the resulting product is attractive for the health care system, as the costs are typically reduced when compared with personalized therapies manufactured “on demand”.
- Outstanding data on generation and characterization of cells which truly recapitulate restoration of the cartlidge. Chondrospheres which are off-the shelf product: this is very strong and convincing.
- Unmet medical need exists.
- The transcriptional comparison of the product with fetal and pediatric AC is adequate as it constitutes a “benchmark” tissue to recapitulate in vitro. The resulting immunophenotypification of committed pre-chondrocytes from human PSC after maintenance constitutes a valuable technique to identify and use of a truly hyaline-type of AC progenitor. The expression of Lubricin by the implanted cells in a rat model of AC defect is of special interest.
- The xeno-free conditions to generate the product alleviate major concerns related with potential biological contaminants remaining in the product. This is considered important by FDA and other regulatory agencies (e.g.: EMA).
- Solid data is presented to support future development.

Concerns

- The team should consider scalability and the complexity of the manufacturing process. There are a number of issues that should be addressed. Having a process with 3 negative selection steps will be a challenge from a cost and scalability issue. Aggregate formation in plates will also be a big challenge for scalability.
- The site of transplantation is not likely to provoke an immune response. This is good from the standpoint of rejection, but could pose issues if a teratoma is formed.
- Concern about use of only one ESC line for derivation.
- Concern about degree of tumorigenic ESC that could be carried through to final product.
- Concerns about a potential for tumor development.
- Scale up and cryopreservation at this stage with acceptable traits is important and perhaps not quite there.
- Safety (tumorigenicity) studies should be performed early- or at least as soon as the production process is "locked".
- Seems to require additional work on scale-up and assessment of residual pluripotent cells in product.
- Need to understand requirements for biodistribution and level of purity of cells and potential number or percentage of undifferentiated cells that could be included in the final product.

Additional Comments

- As a point to be considered (not necessarily a weakness), the use of a single PSC line would narrow the generation of PDC with a particular genetic background, potentially under-representing the entire population of patients.

Application #	TRAN1-09292
Title (as written by the applicant)	Curing Sickle Cell Disease with CRISPR-Cas9 Genome Editing
Translational Candidate (as written by the applicant)	The principal objective of this program is to bring a Cas9-based gene editing cure for sickle cell disease to the pre-IND stage of development.
Area of Impact (as written by the applicant)	The principal barriers to transplant for SCD are lack of a donor and the toxicity of transplant, which can be overcome by the Cas9-based approach
Mechanism of Action (as written by the applicant)	Ex vivo editing of autologous stem cells would be followed by re-implantation of edited cells, bypassing donor requirements and eliminating risks of graft-versus-host disease and rejection. Because sickle RBCs have a markedly reduced lifespan, low level sickle gene correction would be predicted to generate a clinical benefit by virtue of enrichment of the longer-lived corrected RBCs in circulation. After conventional transplant, clinical benefit with as few as 2-5% donor HSCs has been observed.
Unmet Medical Need (as written by the applicant)	Fewer than 1% of individuals with sickle cell disease pursue an allogeneic bone marrow transplant cure today, principally because most affected persons lack a suitable donor. This proposal could make a cure universally available because it corrects the sickle mutation in a persons' own stem cells.
Project Objective (as written by the applicant)	Conduct a pre-IND meeting and prepare a protocol
Major Proposed Activities (as written by the applicant)	• Test Optimal Editing Reagents in stem cells from subjects with sickle cell disease and show correction in >2% sickle stem cells • Translate optimal method for gene editing with GMP-comparable reagents and processes for cell processing and cryopreservation. • Ramp-up testing of reagents to manufacture a demonstration clinical-scale lot of the gene-corrected CD34+ cell product that meets all release criteria
Statement of Benefit to California (as written by the applicant)	Sickle cell disease (SCD) affects over 6000 primarily African-Americans in California. A survival of <40 years of age was observed in a large cohort of California patients. The estimated lifetime cost of care is $9 million per person. This project aims to improve SCD therapy by preparing for a clinical trial that might cure SCD after giving back sickle gene-corrected hematopoietic stem cells to a person with SCD. If successful, this would be a universal life-saving and cost-saving therapy.
Funds Requested	$4,463,435
GWG Recommendation	***Recommended for funding***

Scoring Data

Final Score: 85

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

Mean	87
Median	85
Standard Deviation	2
Highest	90
Lowest	85
Count	13
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	13
Tier 2 (1-84): Not recommended for funding	0

Score Influences

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

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

- SCA is a major health issue. A pre-pre IND meeting has been carried out; thus, the requirements are clear. The investigative team is excellent.
- The FDA comments in prepreIND minutes provide a very clear path forward.
- The team is very strong in basic and demonstrated translational research.
- Small numbers of cells, if delivered and survive, will likely demonstrate some benefit to patients.

Concerns

- Will need to adjust proposal to adequately address FDA concerns.
- Key potential developmental gaps identified with contingencies.

Application #	TRAN1-09293
Title (as written by the applicant)	Injectable pro-regenerative scaffold for treating symptomatic peripheral artery disease
Translational Candidate (as written by the applicant)	Injectable biomaterial derived from the natural scaffolding of porcine muscle
Area of Impact (as written by the applicant)	Improving the quality of life of patients with symptomatic peripheral artery disease.
Mechanism of Action (as written by the applicant)	The proposed mechanism of action is through recruitment of blood vessels and recruitment and differentiation of muscle stem cells. The injected material forms a new porous and fibrous scaffold, which contains appropriate tissue specific cues to stimulate muscle regeneration.
Unmet Medical Need (as written by the applicant)	The prevalence of peripheral artery disease is high in adults and while there are currently some useful symptom improving therapies, there is an unmet need for new therapies for the numerous individuals where these approaches are not successful to improve blood flow and muscle function.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Manufacture product to support nonclinical studies required by FDA • Nonclinical safety studies • Clinical trial planning and development
Statement of Benefit to California (as written by the applicant)	The prevalence of peripheral artery disease is 12% and represents a population that is approximately equal to that of coronary artery disease. The significant reduction in quality of life and high healthcare cost burden necessitates the development of new therapies for these patients. Our injectable biomaterial is a cost effective regenerative medicine strategy to improve blood flow and muscle function, thereby improving patient quality of life.
Funds Requested	$2,607,985
GWG Recommendation	***Not recommended for funding***

Scoring Data

Final Score: 75

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

Mean	79
Median	75
Standard Deviation	4
Highest	88
Lowest	75
Count	15
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	3
Tier 2 (1-84): Not recommended for funding	12

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	8	4	3

Is the rationale sound?	3	5	7
Is the proposal well planned and designed?	1	5	9
Is the proposal feasible?	5	2	8

Reviewer Comments

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

Strengths

- Important problem and sound rationale.
- ECM hydrogel is attractive product concept.
- Reasonable evidence for stem cell mobilization.

Concerns

- Experiments presented do not convincingly show the team is ready for translation.
- Need to present more convincing preliminary data.
- Rat model should have included a comparison of ECM alone, hydrogel alone, then ECM + hydrogel
- Wide error bars on the survival and differentiation data (Fig 3) rendering this data questionable.
- Would be favorable if the applicant can demonstrate that the SKM-ECM is superior to applicant's other related product - this comparison should be done under GLP by a contractor with both GMP-formulations.
- Applicants should have presented more information on related clinical programs from this group.
- It would have been good to have a complete view of the regulatory status of the product and the clinical hold that was related to manufacturing issues. This would have strengthened the argument that the prior clinical experience supports expanding into additional trials.

Application #	TRAN1-09305
Title (as written by the applicant)	Novel combination therapy of repurposed FDA-approved drugs targeting liver cancer stem cells
Translational Candidate (as written by the applicant)	Novel combination of repurposed FDA-approved drugs (SAHA + ATRA) will be studied.
Area of Impact (as written by the applicant)	Cure and safety/toxicity/pharmacodynamics studies for late-stage metastatic hepatocellular carcinoma, cholangiocarcinoma and hepatoblastoma
Mechanism of Action (as written by the applicant)	We first performed drug screening on TICs for the identification of cell-type specific drugs and found that ATRA specifically inhibited cell viability. Additionally, transduction of human TICs with a lentivirus Nanog-GFP reporter was used to perform high-throughput screening for Nanog-inhibitory drugs. SAHA suppressed Nanog expression. Combination of RA with SAHA reduced Nanog expression and inhibited the self-renewal abilities of TICs resulting in apoptosis in vitro and in vivo.
Unmet Medical Need (as written by the applicant)	One goal of targeted cancer therapy is to eliminate all malignant tumor-initiating cells (TICs: namely cancer stem cells: CSCs) and/or circulating tumor cells (CTCs: a tiny fraction of blood cells, often fewer than one in a million) for the prevention of relapse and metasta
Project Objective (as written by the applicant)	Pre-IND meeting and phase I clinical trial
Major Proposed Activities (as written by the applicant)	• Determine efficacy and effective doses for SAHA and ATRA combination treatment in preclinical mouse models (PDX mice and Humanized HCC FRG mice). • Assess clinical safety of the therapeutic • Assess patient subpopulation of responses to the therapeutic
Statement of Benefit to California (as written by the applicant)	The number of Californians have liver cancer due to hepatitis C infection, alcoholic liver disease or cholestatic diseases. Because Hispanics have an increased risk of developing liver cancer (HCC) and alcoholic liver diseases, California, the state with the largest Hispanic population in the US, will be impacted by this epidemic. Thus, developing HCC therapy will not only benefit the Californians suffering by HCC, but may also help the state's medical system to respond to this future challenge.
Funds Requested	$1,485,851
GWG Recommendation	***Not recommended for funding***

Scoring Data

Final Score: 60

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

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

Score Influences

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

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

Reviewer Comments

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

Strengths

- The general approach to identify the combination of previously marketed compounds and the stratification of potentially responsive patients is impressive.

Concerns

- There was limited information presented on the (exclusive) role of NANOG in HCC patients. Likewise, it is not clear by what mechanism ATRA+SAHA is superior to other combinations.
- Product(s) poorly defined - combination therapeutic plus a diagnostic.
- Rationale for the particular diagnostic to stratify patients is weak.
- Preliminary efficacy data is weak.
- Confusing proposal: two different objectives.
- Pre-clinical data not convincing.
- Even though the intent is to re-purpose "FDA-approved" drugs, additional safety testing is needed to determine the appropriate dose, route of administration, and other non-targeted effects for the intended patient population.
- Problems with the approach as well as with the development plan.
- The approach would benefit from developing some proof of concept work.
- Not addressing chemoresistance.

Additional Comments

Additional information in HCC patients would be very helpful and likely more important than the proposed translational experiments in the mouse.

Application #	TRAN1-09310
Title (as written by the applicant)	hESC-derived retina organoids for vision repair in degenerative retina diseases.
Translational Candidate (as written by the applicant)	Human stem cell (hESC)-derived retina organoids, manufactured under GMP conditions.
Area of Impact (as written by the applicant)	Retinal diseases with photoreceptors loss, such as retinitis pigmentosa, age-related macular degeneration, Stargardt disease.
Mechanism of Action (as written by the applicant)	Mechanism of action is based on cell replacement. Transplanted hESC-derived retinal progenitor sheets will mature photoreceptors and integrate with the degenerate recipient's retina. Such transplants have improved visual acuity and responses to flashes of light in the midbrain (superior colliculus) of immunodeficient retinal degenerate rats. Therapies in current clinical trials only target trophic effects.
Unmet Medical Need (as written by the applicant)	This therapy targets retinal degeneration of photoreceptors and dysfunctional RPE, accompanied by vision loss, as seen in advanced stages of diseases such as Retinitis Pigmentosa (RP) and dry Age-related Macular Degeneration (AMD). Current clinical trials only target earlier disease stages.
Project Objective (as written by the applicant)	Demonstration of efficacy, Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Establish a working cell bank; retina organoid product characterization; GLP manufacture implementation; demonstration of purity, stability. • Scale up manufacturing of retinalorganoids under implemented GLP, validate transport; test immunology in vitro. • Preparation for preclinical studies: (1) safety feasibility (standardized methods) and (2) efficacy study in 2 different immunodeficient rat models.
Statement of Benefit to California (as written by the applicant)	Retinal diseases reduce the quality of life of patients, at significant cost to the health care system. The proposed replacement therapy is the only one that targets more mature disease stages of both AMD and RP, for which no other therapy exists. An effective treatment will keep afflicted individuals productive, enhance State tax revenues and defray the healthcare cost burden to taxpayers. It will also lead to robust industry developments, effectively leading to job creation and tax benefits.
Funds Requested	$4,800,901
GWG Recommendation	***Not recommended for funding***

Scoring Data

Final Score: 70

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

Mean	68
Median	70
Standard Deviation	9
Highest	80
Lowest	50
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (1-84): Not recommended for funding	14

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	11	2	1
Is the rationale sound?	4	6	4
Is the proposal well planned and designed?	0	10	4
Is the proposal feasible?	0	7	7

Reviewer Comments

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

Strengths

- The proposed therapy would address a serious unmet medical need given that there are not any therapies currently available for diseases that impact both RPE and photoreceptors. AMD and SD are two major causes of blindness in elderly and pediatric populations.

Concerns

- Inadequate attention to immune rejection of transplant. More experiments should be done to explore this issue.
- Broader range of retinal degenerations should be explored to ascertain generalizability of the results they have so far.
- The number of animals (in the models they have used thus far) demonstrating efficacy is minimal. More experiments should be done.
- Process for selecting organoids should be more rigorously characterized since it currently relies on sampling of selected clones.
- The scientific data supporting this application is inadequate and there is a failure in general to test ways in which this could fail.
- Potential for rejection and the use of only one species for efficacy is a problem.
- Immunological aspects of this transplant are not adequately addressed; animal models not appropriate; needs to consider immunocompetent models.
- Need to identify behavior of organoids on immunocompetent animals.
- The manual method and nondescript clone picking criteria should have been described.
- Immune rejection continues to be a challenge in demonstrating safety and longer-term efficacy.
- There seems to be a major question of immunogenicity of allogeneic transplant in this context.
- Major questions about quality of data demonstrating synaptic integration and basis for modest improvement in visual acuity reported in application.

Application #	TRAN1-09313
Title (as written by the applicant)	Lentiviral Gene Therapy for Bone Repair with Transduced Adipose Derived Stem Cells
Translational Candidate (as written by the applicant)	The efficacy of autologous human adipose derived stem cells transduced with a lentiviral vector containing the cDNA for BMP-2 to enhance bone repair.
Area of Impact (as written by the applicant)	The goal is to create a novel strategy to treat fracture non-unions that do not heal consistently with available therapies.
Mechanism of Action (as written by the applicant)	The use of ex vivo lentiviral gene therapy using transduced adipose derived stem cells) has the potential to revolutionize the treatment of fractures that do not heal. The delivery of an osteoinductive protein (BMP-2) on an osteoconductive scaffold has the biologic potential to induce healing of difficult fractures via autologous transduced human ASCs.
Unmet Medical Need (as written by the applicant)	There are fractures that do not heal with present treatment methods. The delivery of cells that have been genetically manipulated to overexpress an osteoinductive protein (BMP-2) and to be delivered on an osteoconductive scaffold has the biologic potential to heal recalcitrant non-unions.
Project Objective (as written by the applicant)	The goal is to obtain data for a pre-IND meeting.
Major Proposed Activities (as written by the applicant)	• Demonstrate efficacy of proposed ex vivo lentiviral gene therapy using transduced human adipose derived stem cells. • Complete non-clinical safety studies (i.e. biodistribution, vector toxicity, and integrative site sequence analysis) in rat femoral defect model. • Determine "cellular dose" that will be scaled up for human use and assess effects of "worst case" dose.
Statement of Benefit to California (as written by the applicant)	There are citizens in California that sustain serious fractures that do not heal with the therapies that we have today. These injuries may be sustained in car accidents or in combat. A considerable amount of funds are expended in trying to heal these fractures. In addition, prolonged disability leads to loss of wages and depression which also have a financial impact on our society. A therapy that can heal these fractures will reduce medical expenditures and lost wages secondary to disability.
Funds Requested	$3,063,457
GWG Recommendation	***Not recommended for funding***

Scoring Data

Final Score: 70

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

Mean	72
Median	70
Standard Deviation	4
Highest	85
Lowest	70
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	1
Tier 2 (1-84): Not recommended for funding	13

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	8	0	6
Is the rationale sound?	0	10	4
Is the proposal well planned and designed?	1	10	3
Is the proposal feasible?	0	2	12

Reviewer Comments

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

Strengths

- None noted.

Concerns

- Safety issues troublesome.
- Lack of understanding the length of release of BMP and survival of the cells.
- There are difficulties analyzing the pre-clinical studies results, as the summary table presented and the text do not necessarily reflect the same experimental design and resulting data.
- The lentiviral-mediated sustained administration of BMP-2 might be seen as a supraphysiological exposure not in quantity (as with rhBMP-2) but in time.
- The “easy harvest” and the different percentage of MSC per gram of tissue (fat vs bone marrow) arguments are not solid enough given that these cells need to be expanded in vitro in any case.
- Need to explain rationale for adipose instead of bone marrow cells.
- Should demonstrate safety and early efficacy in a large animal model, if possible.
- Overexpression of a single growth factor is over simplistic and not likely to be the one "magic bullet" to address this very serious disease.
- Would have anticipated some follow-up safety data on use of BMP (current literature or use in clinical practice).
- Survival of the cells in the tissue microenvironment is a potential problem.

Application #	TRAN1-09317
Title (as written by the applicant)	Tissue Engineered Tracheal Regeneration and Repair
Translational Candidate (as written by the applicant)	Donor trachea will be decellularized then recellularized with the patient's cells to ensure it is not rejected upon surgical implantation
Area of Impact (as written by the applicant)	Severe tracheal narrowing resulting from inherited or acquired diseases that cause significant impairment to quality and/or duration of life
Mechanism of Action (as written by the applicant)	The objective is to remove the area of tracheal narrowing and replace with healthy trachea with the patient's own cells and that can restore normal breathing and speaking, and eliminate the need for repeated stents and surgical procedures.
Unmet Medical Need (as written by the applicant)	Tracheal narrowing can occur due to congenital diseases or acquired causes across age groups. Multiple surgical procedures have been minimally effective in long-term restoration of tracheal patency and basic functions such as breathing remain compromised emphasizing that new treatments are needed.
Project Objective (as written by the applicant)	FDA Type C meeting
Major Proposed Activities (as written by the applicant)	• Evaluate the length of the graft that can be effectively replaced in juveniles and adults • Assess long-term durability of the graft • Engage the FDA in communications and discussions
Statement of Benefit to California (as written by the applicant)	The overriding objective is to bring a safe and effective solution to narrowing of the trachea that can result in airway obstruction and can be life threatening. Approximately 200 individuals in California alone are plagued with these problems which significantly impacts quality of life. Our current data suggests the approach we propose is a viable solution and will provide significant benefits to patients in desperate need of new life-saving therapies.
Funds Requested	$5,255,860
GWG Recommendation	***Not recommended for funding***

Scoring Data

Final Score: 70

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

Mean	70
Median	70
Standard Deviation	8
Highest	85
Lowest	50
Count	15
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	1
Tier 2 (1-84): Not recommended for funding	14

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	7	4	4
Is the rationale sound?	2	9	4
Is the proposal well planned and designed?	2	10	3
Is the proposal feasible?	1	6	8

Reviewer Comments

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

Strengths
- Rare disease with huge unmet medical need.

Concerns
- Major concern regarding low degree of epithelialization.
- Unclear that the method of scaffold preparation gives a good environment for recellularization.
- Use of proposed animal model may be limiting number of animals per test group and making it difficult to achieve statistically significant outcomes.
- Poor use of proposed animal model. Experiments are inadequately powered to answer questions posed by the investigators. Largely ignores limitations already identified in TE tracheas including poor mucociliary clearance and aspiration, stenosis secondary to excessive granulation tissue, and issues related to poor integration of TE trachea into the host.
- Need advice from FDA as to the usefullness of the proposed other large animal models - there is doubt that small animals will help to clear the path to an IND submission.
- Sufficient epithelialization and mucus production are important and where not addressed.
- Decellularization and subsequent reepithelialization methods need to be more clearly defined.
- Strongly recommend performing future animal studies in compliance with cGLP.
- Concerns around clinical therapeutic challenges of cilia and mucous production.

Application #	TRAN1-09322
Title (as written by the applicant)	Cellular therapy designed to delay Huntington's disease progression
Translational Candidate (as written by the applicant)	Human bone marrow-derived mesenchymal stem cells engineered to secrete Brain-Derived Neurotrophic Factor
Area of Impact (as written by the applicant)	Huntington's disease. Our delivery platform could be modified for other neural disorders, and for planned future corrective gene editing therapy.
Mechanism of Action (as written by the applicant)	Levels of BDNF, a growth factor for neurons, are greatly reduced in the brains of HD patients. BDNF has been shown in numerous transgenic HD mouse studies to prevent cell death and to stimulate the growth and migration of new neurons in the brain, and is thus a lead candidate for neuroprotection in HD. We are using human MSCs as delivery vehicles to produce the growth factor BDNF in the affected areas of the striatum, with the goal of slowing disease progression in HD.
Unmet Medical Need (as written by the applicant)	There is no cure for HD, and no treatments to slow progression. Treatments are only palliative. Our product is intended to provide BDNF, which is lacking in HD patients, to the striatum to delay neurodegeneration. Our studies translate the wealth of data from transgenic mice to the human product.
Project Objective (as written by the applicant)	Type C Meeting with the FDA then transfer to GMP
Major Proposed Activities (as written by the applicant)	• Development and characterization of Master and Working Cell Banks of human mesenchymal stem cells for the planned studies, potency assays • Dose finding efficacy studies in transgenic HD models -R6/2 for survival and R6/NSG for neurogenesis. Efficacy studies in R6/2 and R6/NSG for behavior • Evaluate persistence and distribution of cells and BDNF (Retention and molecular studies).
Statement of Benefit to California (as written by the applicant)	Approximately one in 10,000 CA residents has HD. The financial burden of HD is in the billions, and the emotional cost is immeasurable. Health care costs are extremely high for HD patients due to the long progression of the disease, often for two decades. The lost ability of HD patients to remain in the CA workforce, to support their families, and to pay taxes causes additional financial strain on the state's economy. Our proposed therapy is designed to delay disease progression.
Funds Requested	$2,958,420
GWG Recommendation	***Not recommended for funding***

Scoring Data

Final Score: 50

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

Mean	--
Median	--
Standard Deviation	--
Highest	--
Lowest	--
Count	13
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0

Tier 2 (1-84): Not recommended for funding	13

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	7	4	2
Is the rationale sound?	0	9	4
Is the proposal well planned and designed?	0	10	3
Is the proposal feasible?	0	8	5

Reviewer Comments

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

Strengths

- There remains a strong rationale to test BDNF against Huntington's Disease.
- The laboratory has advanced the translational science of MSC-based cell therapy.

Concerns

- The underlying premise (scientific rationale) for this product (MSC/BDNF) in Huntington's disease is not solid. Thus, it is unclear that intrastriatal transplants of MSCs have beneficial effects in Huntington models and to the extent that they do, it is uncertain that they need to produce BDNF.
- The proposed outcome measures (e.g. measuring intensity of doublecortin immunofluorescence) are too rigorously linked to the suggested biological change (e.g. increased neurogenesis). State-of-the art measures of neurogenesis, and methods to quantify it, must be employed.
- All prior data using the product come from one laboratory, and before entering a phase of clinical translation, experiments should be conducted in a different, independent laboratory.
- The dose response is very narrow, with only the middle range of cells showing benefit. Determining the correct dose requires doing studies in another model and/or mouse strain to determine if the dose is universal or modified by the host. In the latter case, a way of determining dose is needed.
- There needs to be greater information on the neuronal populations that may be affected, not just DCX staining. Moreover, it appears the parental cells are more effective than BDNF-expressors in increasing DCX expression, which makes the therapeutic rationale quite weak.
- What happens to the cells when they disappear? What happens if there is a need for constant BDNF?
- Data on therapeutic efficacy is much too limited.
- There is some concern regarding convincing data to support added value of BDNF.
- There is some concern that the applicant has not considered previous comments from previous CIRM reviews.
- There are multiple weaknesses in available data to support MSC delivery of BDNF for this condition - reviewers pointed out that present data does not give good evidence for neurogenesis in HD models with the MSC/BDNF product.
- FDA apparently had similar concerns.
- A single delivery of MSC expressing BDNF is unlikely to be sufficient as a long-term, definitive therapy.
- A poorly characterized cellular therapy (and in this case cell and gene therapy) is a very risky endeavor especially if defining a dose is so challenging.

Application #	TRAN1-09326
Title (as written by the applicant)	Human embryonic stem cell-derived natural killer cells for cancer treatment
Translational Candidate (as written by the applicant)	Human embryonic stem cell (hESC)-derived natural killer (NK) cells to target relapsed/refractory Acute Myelogenous Leukemia (AML)
Area of Impact (as written by the applicant)	hESC-derived NK cells provide a novel and potent approach to treat relapsed or refractory AML that is resistant to current chemotherapy options.
Mechanism of Action (as written by the applicant)	hESC-derived NK cells provide a standardized, homogeneous, off-the-shelf cellular immunotherapy product that can be used as an allogeneic adoptive transfer treatment for patients with AML who have either never achieved remission with standard induction therapy, or who relapse after previous chemotherapy. hESC-derived NK cells kill tumor cells by several mechanisms: direct cytotoxicity, antibody-dependent cell-mediated cytotoxicity, induction of apoptosis and production of cytokines.
Unmet Medical Need (as written by the applicant)	Five year survival for AML remains less than 30%. Over 10,000 in the US die each year from this disease. Allogeneic NK cells are known to destroy AML cells in patients who have failed chemotherapy. hESC-derived NK cells can provide the first standardized immunotherapy to treat this deadly disease.
Project Objective (as written by the applicant)	The objective is to have an FDA Pre-IND meeting.
Major Proposed Activities (as written by the applicant)	• We will use the GMP hESC line ESI-017 to produce a Master Cell Bank and Working Cell Bank of NK cells using defined clinical-scale cell methods. • We will demonstrate ESI-017 hESC-derived NK cells kill AML tumor cells 1) in vitro, and 2) in vivo using an NSG mouse xenograft approach. • We will assess safety of ESI-017 hESC-derived NK cells using immunodeficient mouse models to test tumorigenicity.
Statement of Benefit to California (as written by the applicant)	Over a thousand Californians are diagnosed with Acute Myeloid Leukemia (AML) each year, and five year survival in California is less than 30%. New treatment options are desperately needed for patients who fail standard chemotherapy. We will produce a standardized, off-the-shelf immunotherapy cell product that can induce remissions and lead to cure of AML. These studies with hESC-derived NK cells will allow Californians to be at the forefront of this cellular immunotherapy approach to treat AML.
Funds Requested	$4,518,815
GWG Recommendation	***Not recommended for funding***

Scoring Data

Final Score: 75

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

Mean	78
Median	75
Standard Deviation	5
Highest	85
Lowest	70
Count	13
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	3
Tier 2 (1-84): Not recommended for funding	10

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	13	0	0
Is the rationale sound?	6	3	4
Is the proposal well planned and designed?	3	8	2
Is the proposal feasible?	4	5	4

Reviewer Comments

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

Strengths

- AML is a deadly disease in need of new therapies.
- NK cell therapies have demonstrated some success in previous studies.
- The development of ES-derived NK cells has been pioneered by the PI.

Concerns

- Many advantages of the product but concerns about off target effects, inadequate animal models for testing toxicity and off target effects and about feasibility in time allocated.
- For CMC, look at purity of undifferentiated cell contamination- so efficiency of separation.
- Need to perform mouse NK (ips-derived) into immunocompetent mice (with and without AML).
- Lack of conviction that the study will produce an important advancement with the project submitted.
- Issues of mismatch of implant producing toxicity.
- Need more time and focus on pre-clinical testing, and time to prepare the data required for pre-IND meeting.
- Insufficient information on efficacy and potential risks associated with complete MHC mismatch between donor product and recipient patients.
- A more appropriate animal model selection would have contributed to a more successful score- use of NOD/SCID mice with K562 xenograft and hu NK cells.

Application #	TRAN1-09353
Title (as written by the applicant)	Stem Cell gene therapy to restore blood flow in critical limb ischemia
Translational Candidate (as written by the applicant)	Human mesenchymal stem cells [MSC] transduced by a lentiviral vector to secrete supraphysiologic levels of vascular endothelial growth factor 165A.
Area of Impact (as written by the applicant)	Subjects with a clinical diagnosis of Critical Limb Ischemia, Rutherford category 4 or 5, who have failed traditional revascularization treatments.
Mechanism of Action (as written by the applicant)	MSCs are established angiogenic agents with a strong safety profile in clinical trials, but have shown limited success in treating vascular disorders. VEGFs are ideal for promoting therapeutic angiogenesis, but sustained delivery in the damaged tissue has not been accomplished. We propose combining the stem cell and gene therapy approaches. Intramuscular injection of MSC/VEGF delivers local and sustained expression of VEGF to promote angiogenesis and local reperfusion of the ischemic tissue.
Unmet Medical Need (as written by the applicant)	Critical limb ischemia (CLI) represents a significant unmet medical need without any effective medical therapies for patients at high risk of amputation. Currently the only method of treatment for this very severe form of CLI is amputation. Costs and risks associated with limb amputation are high.
Project Objective (as written by the applicant)	Preparation for a Type C Meeting with the FDA
Major Proposed Activities (as written by the applicant)	• Develop, characterize, and evaluate cell banks of MSC/VEGF. • Dose Finding Studies in clinically relevant mouse models. • Evaluate the distribution and persistence of cells and VEGF after treatment.
Statement of Benefit to California (as written by the applicant)	Critical limb ischemia represents a significant unmet medical need with no effective therapy for patients at high risk of amputation. Treatment results in a high economic burden to the healthcare system and the state. As a mechanism to treat this disease we engineered Mesenchymal Stem Cells (MSC), effective delivery vehicles for ischemic tissue, to produce high levels of Vascular Endothelial Growth Factor (MSC/VEGF), to enhance formation of new blood vessels. The goal is to prevent amputation.
Funds Requested	$2,577,936
GWG Recommendation	***Not recommended for funding***

Scoring Data

Final Score: 80

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

Mean	76
Median	80
Standard Deviation	12
Highest	85
Lowest	50
Count	13
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	3
Tier 2 (1-84): Not recommended for funding	10

Score Influences

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

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

- Important clinical problem and unmet medical need.
- Excellent GMP plan.

Concerns

- Need to present data on a more translatable model than the mouse.
- Why stem cell approach if multiple parenteral administration of VEGF and other factor could suffice.
- After discussion with the panel-concerns that other cells such as SVF could be used without engineering-and extremely positive results in exploratory studies in patients.
- Modest preliminary data.
- Problems with using immunocompromised animal models; lots of competition in the field; issue of delivery of this therapy; how to extrapolate from a mouse to human.
- Concern about likely benefit (prelim data not very compelling).
- Competition with other cell fractions (SVF).
- Duration of response needs to be assessed.
- Data of Fig 4 show essentially no extra value to transducing VEGF gene into MSC over unmodified MSC. This completely undermines basis to fund the proposal.
- The hindlimb ischemia rodent model has inherent challenges with interpretation of benefit due to the propensity of spontaneous forming of collaterals- this contributes to large variations due to the model which requires powered animal studies to demonstrate efficacy.
- Perhaps an alternative ischemic animal model would assist in making a more subtle step demonstrating efficacy prior to launching into the human clinical setting.

Application #	TRAN1-09365
Title (as written by the applicant)	Development of an Effective Mobilizer of Stem Cells
Translational Candidate (as written by the applicant)	A new effective stem cell mobilizer
Area of Impact (as written by the applicant)	Patients with multiple myeloma and non-Hodgkins lymphoma who need hematopoietic stem cell transplantation
Mechanism of Action (as written by the applicant)	The candidate specifically blocks the interaction of CXCR4 on hematopoietic stem cells (HSCs) and its natural ligand SDF-1a expressed by stromal cells in bone marrow. Disruption of SDF1a/CXCR4 interaction causes the release of HSCs and hematopoietic progenitor cells (HPCs) from bone marrow into the peripheral circulation.
Unmet Medical Need (as written by the applicant)	There is an urgent need for new effective stem cell mobilizers. We propose to develop such products that will benefit patients with multiple myeloma and non-Hodgkins lymphoma.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Additional binding studies through a panel of receptors & functional studies to further confirm the receptor selectivity • Time-response, dose-response, response of multiple treatments and long-term repopulation studies in mice & autologous transplantation study in large preclinical model • Preliminary toxicity studies(acute/chronic toxicity studies, immunogenicity study et al) & PK study (plasma protein binding, biotransformation et al)
Statement of Benefit to California (as written by the applicant)	Autologous hematopoietic stem cell transplantation (HSCT) is an effective therapy for the blood and bone marrow cancer. The most common indications for HSCT in the U.S. are multiple myeloma and lymphoma, accounting for 52% of all HSCTs. If the candidate is commercialized, it may increase the success rate of HSCT in patients with multiple myeloma and non-Hodgkins lymphoma in California.
Funds Requested	$2,945,300
GWG Recommendation	***Not recommended for funding***

Scoring Data

Final Score: 68

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

Mean	66
Median	68
Standard Deviation	6
Highest	80
Lowest	60
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (1-84): Not recommended for funding	14

Score Influences

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

negative, or neutral influence for each criterion is shown.

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

Reviewer Comments

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

Strengths

- A candidate has been identified.
- A rational plan has been presented.

Concerns

- The ultimate utility of the compound is unknown.
- There may not be a need for yet another mobilizer from the clinical perspective. Advantages not clear.
- The proposed product is unlikely to impact an unmet medical need as there is already an available therapy (Plerixafor) used for the mobilization of stem cells during HSCT.
- It is unclear from the proposal if the drug candidate or one of its derivatives will have superiority over Plerixafor or competitor drug candidates in Phase 2 clinical trials (TG-0054 and AMD070).
- Essentially this is a "me too" drug, even if a good one. Value proposition for use in stem cell mobilization, relative to existing approved methods is not sufficient to support funding.
- Other indications may have more clinical significance.
- Attractive proposal but not for stem cell application.
- Maybe not a huge need/impact.

Application #	TRAN1-09394
Title (as written by the applicant)	Human iPSC-derived GABAergic Progenitors for Alzheimer's Disease Treatment
Translational Candidate (as written by the applicant)	Human iPSC-derived GABAergic interneuron progenitors.
Area of Impact (as written by the applicant)	Alzheimer's disease and related conditions.
Mechanism of Action (as written by the applicant)	Transplantation of human iPSC-derived GABAergic progenitors, which will develop into mature GABAergic interneurons, to replace the lost GABAergic interneurons in the hippocampus of AD brains and related disorders.
Unmet Medical Need (as written by the applicant)	As a complex disease that damages the hippocampus, a brain region essential for cognition, Alzheimer's disease presents unique challenges for developing traditional therapies. iPSCs provide a way to generate brain cells for cell-replacement therapy.
Project Objective (as written by the applicant)	Pre-IND
Major Proposed Activities (as written by the applicant)	• Establish a robust differentiation protocol for deriving GABAergic progenitors from human iPSCs. • Short-term efficacy and safety tests of human iPSC-derived GABAergic interneuron progenitors. • Long-term efficacy and safety tests of human iPSC-derived GABAergic interneuron progenitors.
Statement of Benefit to California (as written by the applicant)	Alzheimer's disease (AD) is the leading cause of dementia in California. Currently, there are over 480,000 AD patients in California—more than in any other US state—costing over $20 billion USD in healthcare each year. This research project focuses on developing cell-replacement therapies for AD. Successful completion of this research could help to improve the health of Californians and reduce the adverse impact of AD, thereby increasing productivity and enhancing quality of life.
Funds Requested	$5,944,681
GWG Recommendation	***Recommended for funding***

Scoring Data

Final Score: 90

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

Mean	89
Median	90
Standard Deviation	2
Highest	90
Lowest	85
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	14
Tier 2 (1-84): Not recommended for funding	0

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	14	0	0
Is the rationale sound?	14	0	0
Is the proposal well planned and designed?	13	0	1
Is the proposal feasible?	11	0	3

Reviewer Comments

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

Strengths

- This is an interesting proposal which does have the potential to lead to effective treatment.
- The proposal is based on a solid body of data (in part published in peer-reviewed publications) that transplantation of iPSC-derived GABAergic interneurons restores learning and memory in relevant transgenic mice (apoE4 knockin mice) for Alzheimer's disease.
- Good powerful preclinical data albeit demonstrated in two mouse models.
- Good POC data and opportunity for PD marker should assist in dose selection.
- The PD marker is a strength. Solid proposal.
- Exactly the kind of high risk/high reward stem cell-based approach that CIRM exists to support.

Concerns

- A key issue with the proposal is the potential translatability of the mouse data to humans. The approach focuses uniquely on the role of the hippocampal hilus in memory functions. However, Alzheimer's disease is a disease of the cortex and the hippocampus. The dominant pathology is believed to be that of the cortex. Transplantation of cells in the hippocampus alone may produce a small effect only.
- The practical translatability from mice to humans is a concern. The size of the human hippocampus may make the surgical application of stem cells very difficult. The human hippocampus is a sausage-like structure about 7cm long and 2cm wide. It is not clear how many stereotaxic injections will be necessary to cover the entire area, and how much spreading of cells from individual injection sites is expected.
- Reviewer raised important question of how to deliver cell product to regions of human brain to have best chance for efficacy - differences from rodent should be addressed. This raises concern about feasibility for translation & should be addressed.
- A major safety issue for translation is the risk of injection-related injury, especially with multiple injections as would be required for the human hippocampus.
- Injections of very small volumes cause tissue cleavage at the boundary between the granule cell layer and the hilus, causing extensive degeneration of dentate granule cells due to axotomy.
- Delivery of the cells to human hippocampus is problematic.
- There's a main concern related with the purity of the end product in terms of percentage of differentiated cells.

Additional Comments

- Applicant could benefit from a prepreIND to support scope of preclinical program as well as readiness for embarking on GMP production.
- The team could benefit from a regulatory consultant with specific translational cell-based therapy expertise

Application #	TRAN3-09311
Title (as written by the applicant)	Novel Device for Stem Cell Delivery into Brain Tumors
Translational Candidate (as written by the applicant)	A novel surgical device that is capable of removing brain tumors, and allowing for direct injection of anti-cancer stem or immune cells into tumors.
Area of Impact (as written by the applicant)	Delivery of large number of cytotoxic anti-cancer stem cells or engineered immune cells into the brain is not possible with current technology.
Mechanism of Action (as written by the applicant)	The automated robotic Device is capable of detaching, fragmenting, cauterizing and aspirating brain tumor tissue through a small channel. The cavity generated in the tumor by the Device can then be used to dislodge large number of anti-cancer cytotoxic stem cells or engineered immune cells (T cells) directly into the residual tumor mass. This technology will allow for delivery of larger number of anti-cancer cells, which will improve the efficacy of these cell-based therapies for brain cancers
Unmet Medical Need (as written by the applicant)	Even with standard multimodal therapies with surgery, chemo and radiation, most patients with malignant gliomas (glioblastoma) live less than two years after the initial diagnosis. This Device will have significant impact as it allows for direct delivery of cytotoxic biologic agents into tumors.
Project Objective (as written by the applicant)	Pre-IDE meeting
Major Proposed Activities (as written by the applicant)	• IDE Design Phase
Statement of Benefit to California (as written by the applicant)	We propose to develop a novel neurosurgical instrument that will allow for rapid and safe removal of brain tumor tissue using minimally invasive techniques. The cavity generated by the instrument can then be used for delivery of novel therapeutics directly into tumors. Successful development of this instrument will have a direct impact on public health by providing alternative therapies for malignant tumors.
Funds Requested	$2,193,342
GWG Recommendation	***Not recommended for funding***

Scoring Data

Final Score: 60

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

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

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the

RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

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

Reviewer Comments

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

Strengths

- Unmet medical need, potentially enabling in an aggressive disease setting. It has also been challenging to get drug across the blood/brain barrier.
- Device is quite elegantly designed. The team has done a great job of developing it through iterative testing.

Concerns

- The proposal remains completely opaque as to the chance of injected cells (e.g., CAR-T cells, neural stem cells, etc,) to survive and migrate out of the cavity, following injection in a highly inflamed milieu with blood and debris. This is a major issue that should be addressed.
- Another key issue pertains to back flow. The device offers a very minor solution: place a piece of gelfoam over the hole. Gelfoam is highly porous and permeable. In fact, the reason other delivery methods have failed, is in part due to back flow, which was largely managed with gelfoam. The gadolinium images show some contrast retention, but this imaging is not sensitive to microleaks, which likely get diluted in the CSF.
- The device and the procedure seem to be directed at a one time treatment. The PI mentions briefly that an Ommaya reservoir can be placed at the end of the procedure, for future use. Obviously a debris filled cavity (from dying brain tissue) will result in clogging of the holes of the reservoir catheter, in all likelihood, a problem that is a key impediment to current delivery methods, as recognized by the author.
- Absence of convincing data that the cavity created is adequate to hold stem cells in place and is an effective way to treat metastatic gliomas.
- It is not clear that the contract manufacturers such as Omnica and others have regulatory experience in taking a device thru approval process. If they have such experience, it should be clearly disclosed in the application.
- The applicant did not address previous CIRM concerns about the scientific basis of the proposed therapy, such as cell survival in the lesion site, capacity to target cells far removed from the site of the cavity, the effects of steroids on such cells, etc.
- Funding this device without a clear cut therapy for which it would be used is not compelling.
- The studies on a normal model, instead of seeking out the opportunity to demonstrate therapeutic utility in a model with glioblastoma, do not address the previously expressed concerns.
- No preclinical information regarding efficacy.
- Therapeutic cell distribution and survival is questionable in the harsh (e.g., necrotic) in vivo environment.
- Single injection may not be the holy grail. Therefore multiple injections are likely going to be required as a definitive therapy/treatment.
- The current standard of care is confirmed by experts to be the surgical removal of the tumor bulk rather than hollow and damage the inner core of the solid tumor to serve as a pocket to house a cell therapy.
- The concept of the biodistribution of a cell therapy to migrate to the tumor origin (source) seems unrealistic; especially since this is not sufficiently supported by data.

Additional Comments

- It is important to commend the extraordinary efforts by the PI to conceptualize and produce this device prototype. This reviewer is well aware of the obstacles one faces in developing such an intricate new device. The PI is encouraged to address even summarily the questions of efficacy discussed above. They will be crucial to the success of his endeavor, at IDE presentation or later.
- Strongly suggest doing pre-clinical studies in animal models before approaching the FDA, so that efficacy and safety of the method can be tested.

Application #	TRAN4-09420
Title (as written by the applicant)	Sample pre-enrichment integrated with FACS to improve high purity cell isolation for the discovery and development of stem cell based therapies
Translational Candidate (as written by the applicant)	A Pre-Enrichment Tool that integrates with FACS to isolate cells from complex samples with high purity, throughput, yield, and ease of use
Area of Impact (as written by the applicant)	Stem cells from complex samples will be much easier and faster to analyze or isolate using the proposed tool, for research or cell therapy production
Mechanism of Action (as written by the applicant)	Labeled cells are 1) pre-enriched by magnetic separation, 2) concentrated and washed with debris removal by acoustic focusing, and 3) analyzed or sorted by multicolor FACS. These run as a single process and protocols can be customized for a variety of stem cell applications. Magnetic and fluorescent antibody conjugates are used for cell labeling. The Pre-Enrichment Tool reduces cell handling steps relative to standard methods and creates an optimal sample for FACS.
Unmet Medical Need (as written by the applicant)	Researchers and therapy developers face challenges in quickly and easily isolating highly pure cell populations from complex starting samples. The Pre-Enrichment Tool provides a single streamlined workflow for high speed, high purity cell isolation for research and cell therapy production.
Project Objective (as written by the applicant)	Readiness for transfer to manufacturing
Major Proposed Activities (as written by the applicant)	• Design and develop sub-systems: i) fluidics with magnetic separation and acoustic focusing, ii) automated control and electronics iii) instrument • Integrate sub-systems into new prototype, perform QC and characterization testing including complex biological samples • Perform beta testing in collaboration with stem cell researchers and cell therapy developers
Statement of Benefit to California (as written by the applicant)	The Pre-Enrichment Tool will provide new capabilities for the discovery and development of a broad range of stem cell based therapies, improving the likelihood that new therapies reach the clinic and offer medical benefits to Californians. Beta testing with California scientists will help keep California science at the leading edge. The project will be done in California and may result in a product manufactured in California for sale globally, providing jobs and tax revenue.
Funds Requested	$1,286,185
GWG Recommendation	***Not recommended for funding***

Scoring Data

Final Score: 70

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

Mean	73
Median	70
Standard Deviation	7
Highest	90
Lowest	60
Count	13
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	1
Tier 2 (1-84): Not recommended for funding	12

Score Influences

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

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

Reviewer Comments

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

Strengths

- The approach of using magnetic separation combined with acoustic focusing in combination with FACS to enable cell purification and concentration sounds elegant.
- The team has the expertise in developing this technology and the proposed plan looks feasible.

Concerns

- There are other methods already in market for isolating pure cell populations. The proposal has not provided convincing arguments why FACs would be a better method for purifying cells compared to other approaches.
- The proposal may not meet the future clinical needs and is mostly designed to meet the research needs.
- Approach is more appropriate for a tool development more than for a therapeutic approach.
- Proposal should focus on development of research tool as clinical applications will come later.
- There is no convincing evidence presented to show that negative selection is better than positive selection. Also, taking a cocktail of multiple monoclonal antibodies thru GMP manufacturing processes is much more complex than one specific monoclonal antibody in the case of positive selection.
- The proposal does not discuss how the team plans to generate GMP reagents and steps they will take to obtain regulatory approval.