TRAN AWARDS

7/24/19

$30,713,103 GWG RECOMMENDED

$20,000,000 AMOUNT AVAILABLE

$0 BOARD APPROVED

							Score Range		Number of GWG Votes						
APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Resubmission	Previous CIRM Funding	Disease Indication	Product Type	Approach
TRAN1-11536	Ex Vivo Gene Editing of Human Hematopoietic Stem Cells for the Treatment of X-Linked Hyper-IgM Syndrome	$4,896,628	Y	92	92	3	85	95	15	0	N	Y	X-Linked Hyper-IgM syndrome	Cell and gene therapy	Ex vivo gene corrected autologous hematopoietic stem cells for transplant
TRAN1-11532	PRPE-SF, polarized hESC-derived RPE Soluble Factors, as a Therapy for Early Stage Dry Age-related Macular Degeneration	$3,733,556	Y	88	86	5	70	90	13	2	N	Y	Dry age-related macular degeneration	Biologic	Soluble factors from hESC-derived retinal progenitor cells for intravitreal delivery
TRAN1-11579	Human Embryonic Stem Cell-Derived Neural Stem Cells for Severe Spinal Cord Injury (SCI)	$6,235,897	Y	85	85	4	75	90	12	3	Y	Y	Spinal cord injury	Cell therapy	hESC-derived neural stem cells in an optimized graft for transplant
TRAN1-11548	An optimized human neural stem cell line (hNSC) for the treatment of traumatic brain injury (TBI)	$4,833,271	Y	85	84	5	70	90	10	4	N	Y	Traumatic brain injury	Cell therapy	hESC-derived neural stem cells for transplant
TRAN1-11628	Human Neural Stem Cells (hNSCs) for neuroprotection in perinatal hypoxic-ischemic brain injury (HII)-Pre-IND-enabling Studies	$4,963,684	Y	85	84	5	70	92	11	4	N	Y	Perinatal hypoxic-ischemic brain injury	Cell therapy	Fetal-derived neural stem cells for neonatal transplant
TRAN1-11555	BCMA/CS1 Bispecific CAR-T Cell Therapy to Prevent Antigen Escape in Multiple Myeloma	$3,176,805	Y	85	83	5	65	88	10	5	N	N	Multiple myeloma	Cell and gene therapy	Bispecific CAR-T cells targeting BCMA and CS1 in multiple myeloma cells
TRAN1-11544	Neural Stem Cell-mediated oncolytic immunotherapy for ovarian cancer	$2,873,262	Y	85	83	6	70	90	9	6	N	Y	Ovarian cancer	Cell therapy	Allogeneic neural stem cells to target ovarian cancer and deliver oncolytic virus
TRAN1-11597	HSC-Engineered Off-The-Shelf CAR-iNKT Cell Therapy for Multiple Myeloma	$5,959,873	N	80	78	5	70	85	2	13	Y	Y			
TRAN1-11547	Cardiac Reprogramming Gene Therapy for Post-Myocardial Infarction Heart Failure	$5,167,212	N	80	77	5	70	84	0	15	N	Y			
TRAN1-11611	Development of a human stem cell-derived inhibitory neuron therapeutic for the treatment of chronic focal epilepsy	$5,246,287	N	78	76	6	60	84	0	15	N	Y			
TRAN1-11571	Pre-clinical development of a small molecule therapeutic for the systemic treatment of osteoarthritis	$2,736,500	N	70	70	8	50	80	0	15	Y	Y			
TRAN1-11617	Small molecule PTP-Sigma inhibitor for human hematopoietic regeneration	$2,787,909	N	70	68	7	60	84	0	15	N	Y			
TRAN1-11569	Lentiviral vector expression of Ube3a for the treatment of Angelman syndrome	$2,400,107	N	70	66	8	50	75	0	15	N	N			
TRAN1-11572	Cross-correction of MPSI by lentiviral vector expression of human IDUA in autologous hematopoietic stem cells	$1,615,643	N	65	61	6	50	65	0	14	N	N			
TRAN1-11545	A Novel Drug for Human Pancreatic Cancer Stem Cell Eradication	$3,939,730	N	-	-	-	-	-	0	15	N	Y			
TRAN1-11616	Human Gingival Mesenchymal Stem Cell-based Treatment of Peri-implantitis	$3,927,007	N	-	-	-	-	-	0	15	N	Y			
TRAN1-11596	RIA-derived skeletal stem and progenitor cells for bone repair	$1,340,057	N	-	-	-	-	-	0	15	N	N			

Application #	TRAN1-11536
Title (as written by the applicant)	Ex Vivo Gene Editing of Human Hematopoietic Stem Cells for the Treatment of X-Linked Hyper-IgM Syndrome
Translational Candidate (as written by the applicant)	Human hematopoietic stem cells that have been gene-corrected at the CD40L gene to treat patients with X-Linked Hyper-IgM Syndrome
Area of Impact (as written by the applicant)	These studies will bring stem cell gene therapy for XHIM closer to the clinic, especially those without an HLA match or infections too severe for HSCT.
Mechanism of Action (as written by the applicant)	The CRISPR/Cas9 platform allows site-specific integration of a corrective copy of the CD40L gene at its normal location, maintaining expression of the corrective DNA under control of natural regulatory elements. Transplantation of gene-corrected hematopoietic stem cells, which are self-renewing and long-lived, produces all blood lineages, including T lymphocytes with restored CD40L expression than can stimulate B cells to produce class-switched immunoglobulin.
Unmet Medical Need (as written by the applicant)	There is no curative treatment for XHIM patients without a bone marrow match or with severe infections. Gene corrected HSC can cure XHIM and provides a therapeutic option for these patients. This proposal will advance the field of stem cell gene therapy and treatment of primary immunodeficiencies.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Characterize clinical grade critical reagents in healthy and XHIM hematopoietic stem cells. Perform clinical scale run and pilot toxicology study. • Assess off-target insertions and deletions caused by CRISPR/Cas9 in additional cell lines and in primary hematopoietic stem cells. • Prepare clinical protocol, investigator's brochure, consent forms, and Pre-IND package. Complete Pre-IND meeting with the FDA.
Statement of Benefit to California (as written by the applicant)	Safe, definitive therapies for XHIM represent an unmet medical need. Allogeneic stem cell transplant is frequently complicated by graft-versus-host disease and worsening of pre-existing infections. Successful demonstration that stem cell gene therapy can safely and effectively cure XHIM will shift the paradigm by which patients will be treated, led by California's position as a leader in the field of gene therapy. This will result in improved patient care in the state and around the world.
Funds Requested	$4,896,628
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

SCORING DATA

Final Score: 92

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

Mean	92
Median	92
Standard Deviation	3
Highest	95
Lowest	85
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	15
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific members of the GWG were asked to

indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 15	• The proposed product will fulfill an unmet medical need. • X-linked Hyper-IgM Syndrome is very rare, and is currently treated by bone marrow transplant. If the proposed therapy works, it would eliminate issues associated with bone transplantation. • This potentially curative strategy matches the CIRM mission and is not likely to be funded elsewhere due to the rarity of the disease.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 15	• The proposed project has sound scientific and clinical rationale. • The preliminary data is strong and justifies continued development of product. The authors have shown reasonable on-target and off-target effects. The preclinical data has shown correction of patient-derived T cells. Whether they can correct CD34+ HSCs remains to be seen but will be proven through this very well-written proposal. • The tight regulation of gene expression is a strength.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 15	• The plan appropriately incorporates feedback from the applicant FDA INTERACT meeting, with well-constructed milestones and endpoints based on the preliminary data presented. • This proposal is a logical extension of this groups' previous work. This method might be important in a number of similar diseases. • While a clinical protocol may be helpful, the applicant should consider proceeding with a detailed clinical synopsis at this stage. The proposed development of a clinical protocol, investigator's brochure, and consent forms should be gated to a successful completion of IND-enabling studies and feedback received from a pre-IND meeting. • A potentially excessive amount of money seems to have been allocated for project management.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 15	• The studies are well organized and sequenced to complete the work in the three year time frame. • The project has a clear path forward with a high chance of success based on a very helpful and informative FDA INTERACT meeting. • The team is appropriately qualified and staffed, and the team members are very highly qualified with excellent track records. • Off-target analysis is always an issue with gene editing, but this team has a good chance of solving these issues. • Given the ultra orphan nature of the disease, future clinical trial enrollment would be important to account for in development planning.
No: 0	*none*

Application #	TRAN1-11532
Title (as written by the applicant)	PRPE-SF, polarized hESC-derived RPE Soluble Factors, as a Therapy for Early Stage Dry Age-related Macular Degeneration
Translational Candidate (as written by the applicant)	PRPE-SF is a preparation of soluble factors from polarized retinal pigment epithelial cells, to support survival of photoreceptors in dry age-related macular degeneration (dAMD).
Area of Impact (as written by the applicant)	dAMD with geographic atrophy (early retinal pigment epithelium (RPE) dysfunction/photoreceptor degeneration) that does not involve the fovea, with visual acuity better than 20/80.
Mechanism of Action (as written by the applicant)	PRPE-SF is composed of multiple neuroprotective and anti-inflammatory factors. The cause of AMD is multifactorial, with both genetic & environmental components. However, not all factors have been defined & targeting the known factors (ex. complement pathway) has not been successful. PRPE-SF does not target one specific mechanism as its multitude of factors may work synergistically via a paracrine effect to provide an optimal microenvironment for photoreceptor survival & function.
Unmet Medical Need (as written by the applicant)	AMD affects over 2 million people nationwide (90% dAMD). The target population for PRPE-SF is patients with dAMD with early geographic atrophy, intended to slow progression of disease. There are no products approved for this target & successful development of PRPE-SF would be a major breakthrough.
Project Objective (as written by the applicant)	To enable an FDA pre-IND meeting for PRPE-SF.
Major Proposed Activities (as written by the applicant)	• Manufacturing Process Development •Finalize manufacturing for transfer to cGMP •Develop release testing analytics •Scale PRPE-SF for Phase 1 clinical trial • Preclinical Development •Assess activity, dose & dose regimen for Phase 1 clinical trial •Examine pilot distribution & safety of final PRPE-SF drug product. • Clinical Trial Planning •Develop clinical plan & protocol synopsis for clinical trial •Hold INTERACT meeting with FDA •Hold pre-IND meeting with FDA
Statement of Benefit to California (as written by the applicant)	AMD is one of the most common causes of blindness in those 50 or older with an estimated 400,000 Californians projected to suffer from AMD by 2020. AMD is a debilitating disease, which results in loss of independence and productivity, increased injury and dramatic decline in quality of life. With a $3 billion economic burden annually in California, PRPE-SF will be developed by California based companies, creating additional jobs for Californians and a treatment for this devastating disease.
Funds Requested	$3,733,556
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

SCORING DATA

Final Score: 88

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

Mean	86
Median	88
Standard Deviation	5
Highest	90
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	13

(1-84): Not recommended for funding	2

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• Dry AMD is an important unmet need without good options for therapy. There is currently no cure for the geographic form of dAMD which affects over 20% of individuals over the age of 75 years. PRPE-SF offers a realistic potential for therapeutic intervention in the early stages of AMD. • The proposed treatment for early stage dAMD would be an advance over other potential treatments being evaluated in a number of labs for the treatment of late stage disease. In addition, the proposed injection delivery would be an improvement over current surgical methods.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• The proposed study is based on extensive preliminary data which support the development of PRPE-SF as a therapeutic product for the treatment of early AMD. • The applicant demonstrated the potential of PRPE-SF in both in vitro and in vivo models. • While the animal models are not perfect the preliminary results are nonetheless very encouraging. • There may be challenges in translating pharmacology data from the rodent-based studies. • The mechanism of action is not well-defined.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 14	• This is a high quality and well-constructed program with realistic timing. It encompasses regulatory issues, base manufacturing to the level of GMP, pharmacokinetics and efficacy and safety culminating in the preparation of a Pre-IND package for the translation of PRPE-SF to the clinic. • The formulation and stability of the soluble factors to be used for transplant into humans needs to be addressed. An appropriate clinical grade vehicle for intravitreal injection of the cocktail needs to be developed. • Dosing needs to be considered. It is unclear whether multiple doses are needed, how many times can re-dosing be done, how well patients would tolerate repeat injections, and whether the timeline and budget would allow for an implantable delivery system, if required. • Developing a potency test may be difficult. The team needs to confirm that monitoring only 5 secreted factors is sufficient for quality control of their product. It is unclear whether all important factors have been identified, which factors are most important, whether the ratios of the mix of factors is important, and whether any key factors are in concentrations too small to measure. • A quality systems review for all reagents and supplies should be added, if not already part of existing plans.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 14	• The milestones are realistic and project outcomes should be achieved within the proposed timelines. • This a productive team, with a lot of experience in translational projects and in developing stem cell-based therapies for AMD. • There are manufacturing issues to solve but reviewers believe this team can address and solve those issues. There is concern about use of non-injectable grade culture medium.

	Applicants should consider collecting the soluble factors in medium which is clinically compatible. • With some potential safety issues, there is concern whether the FDA will allow the product to be tested in relatively healthy, early stage AMD patients. If early clinical studies are only allowed in advanced disease patients initially, efficacy may not be evident and additional funding may be difficult to secure.
No: 0	*none*

Application #	TRAN1-11579
Title (as written by the applicant)	Human Embryonic Stem Cell-Derived Neural Stem Cells for Severe Spinal Cord Injury (SCI)
Translational Candidate (as written by the applicant)	H9 (WA09) embryonic stem cell-derived neural stem cells with a spinal cord identity (H9-NSCsc)
Area of Impact (as written by the applicant)	Severe spinal cord injury
Mechanism of Action (as written by the applicant)	Our candidate therapy for SCI uses human neural stem cells in a gel-like matrix containing growth factors. We aim to fill the injury site with replacement neural stem cells that can form new neural "relays" across the injury to restore function. This approach may potentially treat severe SCI by repairing injured connections, in contrast to other stem cell clinical trials for SCI that only aim to improve the function of axons that are spared by the injury.
Unmet Medical Need (as written by the applicant)	20,000 Americans sustain SCI each year, and more than 300,000 live with chronic injury, extracting a huge physical, emotional and financial toll. There are no therapies to repair the spinal cord. We aim to regenerate the injured spinal cord by "splicing" neural circuits, thereby restoring function.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Generate GMP-compliant H9 ESC Master and Working cell banks (MCB, WCB), as well as GMP-compatible H9-NSCsc MCB and WCBs. • Rodent studies to establish proof of concept and pilot safety. • Develop Chemistry, Manufacturing, and Control (CMC) characterization and release assays for the candidate H9-NSCsc.
Statement of Benefit to California (as written by the applicant)	SCI affects approximately 300,000 people in the U.S., with more than 20,000 new injuries per year. People with SCI often endure decades of severe disability, with staggering physical, emotional, and financial costs. The first year of treatment alone is $1 million for a quadriplegic patient. Better treatments are needed, and even a modest increase in functional capacity (1-2 spinal levels) can produce meaningful improvement in quality of life and cost savings for California.
Funds Requested	$6,235,897
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

SCORING DATA

Final Score: 85

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

Mean	85
Median	85
Standard Deviation	4
Highest	90
Lowest	75
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	12
(1-84): Not recommended for funding	3

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• SCI is a large unmet medical need. While there are a number of different approaches to treat SCI, at this point in time there is no approach that is so advanced that it looks like it's being developed into a product. Any treatments to improve outcomes in spinal cord injury would be welcome and would offer clear economic benefit. • The approach is sound and the potential to form new neuronal relays across an SCI is attractive.
No: 1	• The clinical applicability is unclear. The proposed clinical efficacy endpoints are not compelling and the indication isn't fully developed (thoracic vs. cervical). This isn't critical at this juncture, but these issues will arise and must be addressed going into an IND meeting. The treatment effect sizes proposed may be difficult to prove in a trial.
GWG Votes	**Is the rationale sound?**
Yes: 15	• This is a novel approach with a rational plan. • The growth of new neurons in the various animal models is impressive, but the model may recover on its own, so the functional improvements are small. • There is much more data in this resubmission that supports the selected cell line as a viable option for demonstrating efficacy in human patients. However, the efficacy data is somewhat weak.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 13	• The project is logically organized with sequential tasks directed at IND. • The growth factor cocktail adds complexity and cost to the product, as they will need licenses to access those growth factors. It is encouraging to see they are going to study which ones appear to be most critical, as the increased cost and complexity would be worthwhile for this indication if the efficacy warrants it. • There is some concern that completion of milestones/aims from a prior award should be completed and reviewed before further investment in program. • The CMC program is well planned out. • Optimization of the growth factor 'cocktail' still needs to be done and could delay development. Identity and potency tests are important and could lead to issues down the road if they have yet to identify the appropriate markers.
No: 2	• Aim 1 on this application appears to overlap with an aim on a prior CIRM grant. • The approach for milestone 1 is not clear. Identity and potency tests are important, and the proposal for conducting a 'screen' to identify the appropriate markers suggests the cell type is not yet well understood. The success criteria suggests that there could be a significant number of 'other' cells unrelated to potency. • Optimizing the growth factor 'cocktail' (milestone 2) suggests that the process (and cell phenotype) could change substantially and delay development.
GWG Votes	**Is the proposal feasible?**
Yes: 15	• Developing assays for the detection of residual ES cells may be more difficult and time consuming than they are currently thinking and may lead to time delays getting into the clinic. • A good team with the needed resources. • A dedicated project manager needs to be assigned to this program.
No: 0	*none*

Application #	TRAN1-11548
Title (as written by the applicant)	An optimized human neural stem cell line (hNSC) for the treatment of traumatic brain injury (TBI)
Translational Candidate (as written by the applicant)	Shef6.1 embryonic cells will be enriched for a neural stem cell marker, CD133. These human neural stem cells (hNSCs) are designated as S6.133.hNSCs.
Area of Impact (as written by the applicant)	Shef6.1 human neural stem cells will be tested as a treatment for memory & behavioral deficits resulting from traumatic brain injury (TBI).
Mechanism of Action (as written by the applicant)	Traumatic brain injury (TBI) results in loss of neural tissue and chronic inflammation. Additionally, patients may have chronic cognitive and emotional deficits. S6.133.hNSCs have been shown to improve learning and memory, and reduce anxiety in rodent, via replacing lost neurons and glial cells (via cell replacement or neurogenesis), protecting the injured brain from secondary cell loss (trophic effect), and reducing neuroinflammation (via cytokines), possibly by synergic mechanisms of action.
Unmet Medical Need (as written by the applicant)	TBI is a silent epidemic, affecting 230,000 Californians yearly (comparable to Alzheimer's), and projected to cost CA $9.6 billion per year. TBI can lead to significant chronic deficits, yet there are no approved therapies, whether pharmacological or cell based, and few products in the pipeline.
Project Objective (as written by the applicant)	We are targeting a Pre-IND meeting by month 30.
Major Proposed Activities (as written by the applicant)	• Generate cGMP compatible human neural stem cells (hNSCs) from Shef6.1 embryonic stem cells. Finalize CMC methods and test sterility and stability. • Test efficacy, safety, dose & immunosuppression in male & female Athymic nude rats, and a large animal model of traumatic brain injury • Finalize target product profile (TPP) and Pre-IND documents with clinical team and consultants at iQVIA; schedule Pre-IND meeting with the FDA.
Statement of Benefit to California (as written by the applicant)	Traumatic Brain Injuries (TBI) are the leading cause of disability. Yearly, 1.7 million American's experience a TBI (~230,000 Californians), costing California ~$9.6 billion YEARLY. A cell therapy that could reduce inflammation, replace injured brain tissue, or protect host neurons to improve learning and memory could have significant implications for a patient's quality of life and could significantly reduce the economic impact of TBI on the patient, their family, and the state of California.
Funds Requested	$4,833,271
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

SCORING DATA

Final Score: 85

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

Mean	84
Median	85
Standard Deviation	5
Highest	90
Lowest	70
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	10
(1-84): Not recommended for funding	4

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• This is a huge unmet medical need with some treatments available, but not regenerative methods. There can be lifelong issues once the injury occurs and thus expenses are ongoing and significant. • If the transplants were able to improve outcomes after TBI, this would be of tremendous value for patients and healthcare providers.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• The investigators have shown improved cognition, neuroprotection, and modulation of the host inflammation. • The benefits observed in the animal model used are somewhat artificial as the treatment is for a very specific focal brain model that leads to hippocampal damage. The benefits seen in the animal model may not translate to the typical case in humans, where actual brain injury is not so focal but usually a distributed injury. • The rationale is strong, as NSCs have multiple potential mechanisms of action. As a range of different types of damage occur in TBI, it seems likely that an approach of this general type is going to be required. • The very long period of cell manufacture can lead to changes in the cell. It is unclear how many normal cells they will have.
No: 2	• It is unclear if the parent cell line will be compared to the newly derived line.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 14	• The proposed studies are well considered and planned. • There is little discussion of brain imaging and how the target is selected, and it is unclear whether imaging can be applied to visualize repair. • Obtaining an INTERACT meeting appears unlikely based on advanced stage of the program. In the scenario that the applicant is unable to obtain feedback from FDA, refraining from initiating large animal study or safety study until after receiving FDA feedback on design is strongly recommended, especially considering complexity, cost, and duration of these studies. Moving up the pre-IND meeting is recommended to discuss data obtained from Milestone 3 and gate subsequent activities off of that interaction. • There is significant concern about the prolonged culture time for manufacturing.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 13	• A good team is in place, and resources are in place to carry out the studies. • Some issues may arise with genetic stability of the cells.
ß	*none*

Application #	TRAN1-11628
Title (as written by the applicant)	Human Neural Stem Cells (hNSCs) for neuroprotection in perinatal hypoxic-ischemic brain injury (HII)-Pre-IND-enabling Studies
Translational Candidate (as written by the applicant)	An established stable human neural stem cell line unmanipulated genetically & propagated under defined conditions
Area of Impact (as written by the applicant)	Perinatal asphyxia (also called hypoxic-ischemic injury, HII), a major untreatable cause of cerebral palsy & cognitive disability
Mechanism of Action (as written by the applicant)	hNSCs rescue the penumbra, the part of the brain lesion following perinatal asphyxia that still has viable though endangered cells. Such rescue includes preserving tissue; host neuron growth; revascularization; inhibiting inflammation & scarring. Anatomic & behavioral improvement results. If strategically administered, hNSCs can supply their neuroprotective molecules in a manner that synergizes with standard-of-care, hypothermia, which is only marginally effective but must be offered to babies.
Unmet Medical Need (as written by the applicant)	Perinatal hypoxic-ischemic brain injury is an untreatable common cause of CP & disability. Hypothermia (HT) is standard-of-care for this condition although it is only marginally-effective. Any new trial must include HT. We will coordinate hNSC administration to synergize with HT & improve outcome.
Project Objective (as written by the applicant)	Pre-IND meeting, ultimately a Phase 1b/2a trial
Major Proposed Activities (as written by the applicant)	• Ascertain the proper timing of hNSC administration in relation to hypothermia to achieve synergy • Determine the manufacturing specifications & biodistribution of the hNSCs in anticipation of IND-enabling studies • Preparation of a pre-IND package
Statement of Benefit to California (as written by the applicant)	Perinatal asphyxia occurs in 2-4/1000 births. Despite hyperthermia (which is only marginally effective), 80% of asphyxiated infants develop neurologic signs with 10-20% remaining significantly impaired (e.g., CP; disability; epilepsy). The cost to California economy is $1M/child in terms of lifelong medical & rehabilitative care; the impact on family dynamics is 2-5-fold greater than that. We believe stem cell-based interventions can improve these outcomes.
Funds Requested	$4,963,684
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

SCORING DATA

Final Score: 85

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

Mean	84
Median	85
Standard Deviation	5
Highest	92
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	11
(1-84): Not recommended for funding	4

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 15	• Neonatal HI can be caused by several problems during labor and delivery and the vascular pathology is fairly diverse. Despite the use of therapeutic whole body hypothermia, which is only marginally effective in a subset of babies, most of the infants develop neurologic signs with 10-20% remaining significantly impaired. It would be valuable to have additional treatments with more flexibility in the timing of administration. Given the high survival rates there are lifelong costs associated with these patients. • In the absence of proven neuroprotective drugs, applying stem cells with multiple potential mechanisms of action is a reasonable proposal.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• The preliminary data are supportive and extensive. The PI has over 23 years of data – first with murine NSCs & then with the actual human NSCs to be used in the proposed clinical trials. • The applicants have shown engraftment in both rodent and large animal models. This increases confidence that human engraftment will occur. • Preclinical data is good but neural cells and tissue have not been effective to date and it is unclear how this is an improvement over previous work. • The model used may not mimic the clinical findings in terms of lesion distribution/imaging. It is unclear whether the cells will migrate far enough to be effective, and whether a larger animal test may be appropriate. • The unilateral carotid model results in lesions that differ substantially from those of actual neonatal hypoxia. It will be much more challenging to deliver to the affected regions than in the mouse model. • Injection sites will be more difficult to target in humans than in mice. Better imaging methods than ultrasound are needed. • The applicant mentions several MR techniques such as perfusion imaging. Perfusion imaging generally requires contrast which is not mentioned, and it is unclear whether this is safe in children. The only current alternative to the use of contrast is arterial spin labeling MRI.
No: 2	• It is not clear what benefit this NSC type offers over many of the prior stem cells used in similar attempts over the years.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 14	• Applicant may now be ready for an FDA pre-IND interaction, thus appears relatively low-risk from that perspective. • The development program could be significantly streamlined and accelerated by focusing on those core translational activities necessary to initiate human clinical testing. • Additional dosing studies may be needed. • This is a well designed proposal and will likely answer the question asked, but whether the therapy will work is questionable. • The proposal has a large number of tests and evaluations with only rudimentary mention of a statistical analysis plan. This is concerning and the project would be more compelling if there was input from an experienced biostatistician, as principal component analysis may be useful.
No: 1	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 15	• The timeline appears aggressive but reasonable for the planned studies and goals. • This is a high quality team and likely to be successful. • How the maximum tolerated, maximum feasible and no adverse effect doses will be determined is unclear. Efficacy is very loosely defined as any improvement in a behavioral or functional parameter at 18 months with concomitant improvement in MRI findings.
No: 0	*none*

Application #	TRAN1-11555
Title (as written by the applicant)	BCMA/CS1 Bispecific CAR-T Cell Therapy to Prevent Antigen Escape in Multiple Myeloma
Translational Candidate (as written by the applicant)	A single-chain bispecific chimeric antigen receptor (CAR) targeting BCMA and CS1 will be used to in autologous T-cell therapy for multiple myeloma.
Area of Impact (as written by the applicant)	Translational candidate will enable treatment of patients with heterogeneous or BCMA– multiple myeloma and prevent cancer relapse due to antigen loss.
Mechanism of Action (as written by the applicant)	BCMA and CS1 are markers commonly found on multiple myeloma (MM) cells. Here, patient-derived naïve/memory T cells enriched in stem-cell memory phenotype are engineered to express a BCMA/CS1 bispecific chimeric antigen receptor (CAR), which triggers robust T-cell activation and anti-tumor effector function upon recognizing either BCMA or CS1 on the surface of target cells. The bispecific CAR-T cell can efficiently eliminate MM tumor cells even if they had lost expression of either BCMA or CS1.
Unmet Medical Need (as written by the applicant)	Multiple myeloma (MM) is an incurable disease. CAR-T cell therapy targeting BCMA shows clinical promise against MM, but many patients have BCMA-negative tumors or develop BCMA-negative MM after treatment. BCMA/CS1 bispecific CAR-T cells can prevent tumor escape to increase clinical efficacy.
Project Objective (as written by the applicant)	Pre-IND meeting; readiness for GMP manufacturing.
Major Proposed Activities (as written by the applicant)	• Rodent studies to determine optimal T-cell dosing regimen and compare BCMA/CS1 bispecific CAR with bb2121 (a clinically tested single-input BCMA CAR) • Cell-culture and rodent studies to identify any propensity for the Therapeutic Candidate to cause cytokine release syndrome and off-tumor toxicity • Demonstration of GMP-compatible cell manufacturing and completion of clinical protocol and internal regulatory filings
Statement of Benefit to California (as written by the applicant)	Multiple myeloma afflicts >32,000 new patients in the US and leads to >1,200 deaths in California each year. A therapy with robust and durable efficacy against this otherwise incurable disease will not only improve the well-being of Californians, but also reduce the substantial medical costs associated with long-term and ultimately ineffective treatments. This will reduce burden on the state's medical system and enable redirection of resources to other areas of unmet needs.
Funds Requested	$3,176,805
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

SCORING DATA

Final Score: 85

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

Mean	83
Median	85
Standard Deviation	5
Highest	88
Lowest	65
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	10
(1-84): Not recommended for funding	5

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific members of the GWG were asked to

indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• While the CAR-T field has made lots of advances, there remain many challenges, and this program can answer many important questions for the field and provide a big impact for patients. • The project is designed to generate second generation CAR-T cells targeting two antigens. Multiple myeloma treatment currently includes several novel targeted agents. It is likely that bb2121 (anti-BCMA CAR-T) will be approved soon, however, early data suggest that this approach is not durable in most patients. The major unmet need in the disease is the availability of therapies capable of producing prolonged remissions, especially in advanced patients. There is also a need for broadly applicable curative therapies. It is possible that the proposed approach can meet the first unmet need, but unlikely to address the second.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 10	• The bispecific CAR approach would expand the number of patients that could benefit from this treatment and may reduce costs as 2 patients subsets could be treated with a single product. • Both the BCMA and CS1 targets are supported in the literature (and clinical trials) and the rest of preclinical data is good. • The approach to dual targeting with one CAR-T is attractive. While multiple groups have attempted this concept, this application presents an approach that is most likely to achieve success. • There are some doubts about whether CS1 is a target that will likely improve efficacy.
No: 4	• Antigen loss of CS1 may also occur. • It is unclear whether CS1 is a useful target along with BCMA.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 12	• The program is well designed, and based on the previous experience developing a CD19/CD20 CAR. The program is well positioned for success. • The timeline is feasible and the studies are rational and well designed to achieve meaningful outcomes and lead to a potentially successful pre-IND meeting. • The available data does not support enrichment for T memory/stem cells as beneficial for CAR-T efficacy (bulk T-cells will contain requisite subsets). • The data regarding the fratricide experiments is confusing based on the proposed mechanism for how this product works. The results are unexpected and thus more investigation may be needed.
No: 2	• The rationale for the BCMA CAR-T cell and anti-PD1 antibody combination treatment in the proposed preclinical testing is unclear. • The CRS modeling study is not necessary. • CD62L fractionation is not necessary and adds complexity.
GWG Votes	**Is the proposal feasible?**
Yes: 14	• The team has excellent experience in this area. • Manufacturing and other contracts appear to be in place and ready to go. Timelines are appropriate. • The program is considered low-risk in terms of achieving a successful pre-IND meeting. • Additional expertise in the biology of myeloma would be helpful.
No: 0	*none*

Application #	TRAN1-11544
Title (as written by the applicant)	Neural stem cell-mediated oncolytic immunotherapy for ovarian cancer
Translational Candidate (as written by the applicant)	A clinically tested tumor-tropic neural stem cell (NSC) platform for effective distribution of oncolytic virotherapy to ovarian cancer metastases
Area of Impact (as written by the applicant)	This NSC-delivered virotherapy approach will lead to a more efficacious, less toxic treatment for metastatic ovarian cancer and chemoresistant cells.
Mechanism of Action (as written by the applicant)	CRAd-S-pk7 is a tumor specific replication-competent adenovirus driven by a survivin promoter, which is constitutively highly expressed in ovarian cancer cells. We will use our tumor-tropic/tumor-penetrating NSC platform to produce the oncolytic virus within ovarian metastases. Viral replication will lyse cancer cells and infect neighboring cancer cells, thus amplifying its effect until reaching normal tissue. We will also stimulate a secondary immune response to newly exposed tumor antigens.
Unmet Medical Need (as written by the applicant)	Most ovarian cancer patients present late stage with abdominal metastases, and can't complete chemotherapy due to severe toxicity and chemoresistance. NSCs will more effectively target and distribute an oncolytic virus, selectively lysing cancer cells and stimulating an anti-tumor immune response.
Project Objective (as written by the applicant)	Pre-IND meeting; ready for GMP clinical lot.
Major Proposed Activities (as written by the applicant)	• In vivo determination of dosing regimen (multiple rounds) for maximal therapeutic efficacy • In vivo determination of secondary immune response, following oncolysis of tumor cells • In vivo determination of preliminary safety/toxicity profile
Statement of Benefit to California (as written by the applicant)	Ovarian cancer is the most lethal gynecologic malignancy, resulting in 1,500 deaths annually in California. At diagnosis, >70% of patients already have metastases throughout their abdomen, leading to a dismal 34% 5-year survival rate. We anticipate that our stem cell-delivered oncolytic virotherapy will lead to a more effective, less toxic treatment for these patients that will kill even metastatic tumor foci and chemoresistant cells, improving survival of ovarian cancer patients in California.
Funds Requested	$2,873,262
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

SCORING DATA

Final Score: 85

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

Mean	83
Median	85
Standard Deviation	6
Highest	90
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	9
(1-84): Not recommended for funding	6

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in

the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• There is a tremendous unmet medical need for new treatments for recurrent and late stage metastatic ovarian cancer. • If the therapy is successful, it would be important advance that could be used after other methods have been tried. • There is a lot of excitement for this novel approach.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• This project is based on multiple years of studying the ability of NSCs to be used as anti-tumor reagents, and the surprising finding that they also can be applied to the treatment of tumors outside of the central nervous system. • While oncolytic viruses can efficiently infect and kill cancer cells, their delivery is a challenge as most of the population has pre-existing antibody against the vectors. The stem cells in this case are key to the treatment. The data presented in this proposal suggest that the NSC cells are naturally homing to the cancer cells, delivering the virus and allowing the vector to retain its therapeutic efficacy by escaping neutralizing antibodies. • Using a cellular vector to try and protect adenovirus from immune neutralization is an interesting idea, and targeting adenovirus expression to cells with an active survivin promoter would offer a measure of specificity. The applicant says that survivin is expressed in 85% of chemo resistant ovarian cancer patients, but does not discuss whether expression is seen in all cancer cells and particularly whether expression is seen in cancer stem cells. This information would be helpful in understanding the utility of this approach. • The new generation antivirus constructs being employed in this study have been designed to overcome limitations of previous viruses. • The significant reduction in tumor weight demonstrated in Fig 6d is a strength. • The weakness is that they have not demonstrated increased survival of tumor bearing mice. • Will the NSCs be rejected by the patient's innate immune system? It appears this risk is minimized and further examined in this proposal. These studies will be critical in the pre-clinical studies to be sure that NSCs will not be rejected by the innate immune system.
No: 2	• It is unclear if these modified cells will be rejected in humans. There is potential rejection from NK cells given the cells don't express HLAs, which is not discussed in the proposal.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 13	• The project is well designed and based on extensive prior knowledge. The pre-clinical experiments proposed by the team will lead to the selection of the initial dose to be used in the clinical trial. • The studies are well-designed and have a high chance of success. The major hurdle relates to the potential for immune rejection by the NK cell and innate immune compartment. • A meeting with FDA would be helpful to better understand the demonstration of preclinical efficacy that would be required for the FDA to allow an IND and ensure that the planned studies provide that. • It is well planned, but high risk and high reward.
No: 2	• There is an absence of any efficacy data in the proposal which is a critical flaw.
GWG Votes	**Is the proposal feasible?**
Yes: 14	• Continued development appears justified despite the acknowledged challenges of generating supportive pharmacology data in animals. • The path to pre-IND appears reasonable and consistent with FDA expectations. • The PI has previous preclinical and clinical expertise with this platform in another indication. • This is an excellent team that has significantly advanced the field. • All of the pieces are in place to move this project forward efficiently.
No: 1	• Extended survival has not been demonstrated in any animal model. • It is unclear whether the cells will be invisible to the immune system.

Application #	TRAN1-11597
Title (as written by the applicant)	HSC-Engineered Off-The-Shelf CAR-iNKT Cell Therapy for Multiple Myeloma
Translational Candidate (as written by the applicant)	stem cell-based off-the-shelf CAR-iNKT cells
Area of Impact (as written by the applicant)	multiple myeloma (MM)
Mechanism of Action (as written by the applicant)	The proposed therapeutic candidate can directly kill MM tumor cells.
Unmet Medical Need (as written by the applicant)	MM remains an incurable disease, with a high relapse rate. The proposed therapeutic candidate can offer a new treatment opportunity for a broad base of MM patients.
Project Objective (as written by the applicant)	Pre-IND meeting with the FDA
Major Proposed Activities (as written by the applicant)	• Pharmacology study of the therapeutic candidate • Chemistry/Manufacturing/Control (CMC) study of the therapeutic candidate • Safety study of the therapeutic candidate
Statement of Benefit to California (as written by the applicant)	In 2019 alone, it is estimated that over 3000 Californians will be diagnosed with MM, and over 1320 Californians will die of this disease. MM results in devastating economic impacts to the state of California, in addition to the substantial economic and emotional impacts on individual patients and their families. The proposed therapeutic candidate can potentially become a life-saving treatment for MM patients and therefore benefit the state of California.
Funds Requested	$5,959,873
GWG Recommendation	***(1-84): Not recommended for funding***

SCORING DATA

Final Score: 80

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

Mean	78
Median	80
Standard Deviation	5
Highest	85
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	2
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 15	• Multiple Myeloma remains a significant unmet medical need. Several effective therapies such as BCMA CAR-T and T cell antibodies are in clinical development but additional innovative approaches are likely needed. • This off-the-shelf stem cell based therapy is exciting because it could simplify, reduce variability, have lower cost, and increase the utility of CAR therapies for MM.

	• There are still concerns about the ability to develop a clinically relevant product.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• The rationale and approach to development of the product is compelling. • They use an HSC derived system to generate the iNKT cells and BCMA is a validated target for MM. • The value proposition is not clear given the manufacturing challenges.
No: 2	• The target BCMA antigen is clinically validated by other CAR-T programs. The iNKT platform is an exciting CAR approach. • The manufacturing process is extremely complex and hard to scale up. The use of trans-well inserts are only being scaled "linearly" through automated pipetting and is not a closed system. Scale up to full development and commercialization will likely need a complete rework of the process. • It is unclear if HLA deleted cells will be tolerated in humans. • The manufacturing process seems very complex and cumbersome. This is a group that could likely pull this off, but it is still risky.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 9	• This is a well-planned project and the PI has identified all of the key studies. • An INTERACT meeting with FDA is recommended as soon as possible. The FDA may have concerns about the approach, which could significantly slow down this program. • There may be significant challenges with the gene editing that need to be done to produce this product. • There is poor definition of the CRISPR benchmarks and associated analytics. Off-target analysis and cGMP reagents need to be utilized. The hetereogeneity from triple-gene editing of HSCs and its potential adverse events with the HSC pool need to be addressed. • The proposal is well planned but there needs to be some additional input to the manufacturing process. The program is very ambitious with regards to timing.
No: 6	• How long will anti-tumor immune responses for the iNKT cells last? The persistence and duration with measurable anti-tumor immune responses for the iNKT cells need to be defined. • Manufacturing requires attention. The genome editing and scale up issues need more thorough consideration.
GWG Votes	**Is the proposal feasible?**
Yes: 9	• The work does seem feasible. However, this project will likely take a long time given where the project is currently at. The proposed cell manipulations are many: CRISPR out several genes, two times viral vector transduction, positive and negative cell sorting, co-culturing with donor cells and cell line, bead stimulation for further culturing. In totality, this becomes a very daunting project with a lot of reagents. • The major concern relates to the complicated manufacturing process, the use of multiple vectors and gene editing, and minimal feasibility studies demonstrating that they can actually produce the drug product in a reproducible manner. • The extremely complex manufacturing in an open system may pose long-term challenges in late-stage clinical testing and/or commercialization. • The team behind the proposal as well as the facility are world class.
No: 6	• While the proposed work is theoretically feasible, the feasibility of producing this product for clinical use is not clear. • The main concern is that the manufacturing looks extremely complex and it may not turn out to be feasible and certainly will be very, very expensive. However, if efficacy is sufficient, it is a compelling concept and maybe be worth the challenges. • It will be very difficult to scale this manufacturing process, and the manufacturing process is not closed and so subject to contamination with so many wells being used. This could also impact timing and cost of the project. The manufacturing process is also very long. • The project plan and timeline is very short given the complexity of the manufacturing protocols. Given the numbers of steps and reagents (CRISPR, lentivirus, retrovirus) any issues could significantly delay the project.

Application #	TRAN1-11547
Title (as written by the applicant)	Cardiac Reprogramming Gene Therapy for Post-Myocardial Infarction Heart Failure
Translational Candidate (as written by the applicant)	The candidate is a gene therapy that delivers cardiac reprogramming factors to convert resident cardiac fibroblasts into functioning cardiac muscle.
Area of Impact (as written by the applicant)	The targeted condition is heart failure arising from myocardial infarction or other insults causing focal heart muscle loss.
Mechanism of Action (as written by the applicant)	The gene therapy is delivered to the heart where it infects resident cardiac fibroblasts. The genes expressed from the therapeutic viral vector drive direct cellular reprogramming of infected fibroblasts into working cardiac muscle cells. This cell conversion replaces heart muscle that has been lost during ischemic injury such as myocardial infarction, thus restoring heart function and cardiac output.
Unmet Medical Need (as written by the applicant)	In the US, nearly 6 million people are suffering with heart failure (HF). HF is typically initiated by damage or death of functional heart muscle cells, which are not naturally regenerated in the adult heart. This gene therapy would restore those lost cardiac muscle cells and thereby treat HF.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Rat study to test for reprogramming efficacy in chronic myocardial infarction • Yucatan minipig study to test for efficacy or toxicity using two different doses of the cardiac reprogramming gene therapy after myocardial infarction • Dose finding and pilot 4-week tox study in most appropriate model (rat or pig)
Statement of Benefit to California (as written by the applicant)	Heart disease is a leading cause of death in adults and children in California, but there is no current treatment that can promote cardiac regeneration. This proposed research will benefit the state of California by laying the groundwork for a clinical trial that could result in a new therapy for heart disease that generates heart muscle cells from within the heart. If successful, there is potential economic benefit in terms of productive lives saved and in commercialization of this technology.
Funds Requested	$5,167,212
GWG Recommendation	***(1-84): Not recommended for funding***

SCORING DATA

Final Score: 80

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

Mean	77
Median	80
Standard Deviation	5
Highest	84
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• There is excitement about this product and its potential impact as there is a huge unmet need. • The approach is conceptually elegant, and, if successful, would have a major impact on the way ischemic heart failure is treated. The lessons learned here from genetic reprogramming could potentially guide treatments for other similar types of heart disease.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• The data appear supportive of the scientific rationale and justify additional testing. Data from a mouse model suggests a statistically significant incremental improvement in ejection fraction. The existing data should be complemented with in vivo data showing vector biodistribution, transgsene expression, and reprogramming of cells. • Applicant maintains that additional development work to further optimize the capsid and raise dose level will translate to improved outcomes. However, the applicant does not appear to be proposing to do this work.
No: 3	• The published preliminary data with the 5-factor cocktail to reprogram cardiac fibroblasts to cardiomyocytes in mice is interesting, but do not really show a robust improvement in function. The two-factor cocktail is a necessary advance but the efficacy data is even weaker. The treated group doesn't really improve function, but just doesn't get worse. Importantly, they don't show equivalency of groups prior to treatment. • The in vitro work is interesting, but some fundamental studies should be done on the cardiomyocytes produced to determine whether they have electrical activity, whether they contract, and whether they are mature. • Capsid selection and transgene optimization does not appear to be done yet. • The rationale for using AAV5 is not strong. • Some fundamental product design decisions (e.g. route of administration) are yet to be made, which undermines the rationale for moving forward as proposed.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 0	*none*
No: 15	• There are gaps in scientific understanding that need to be resolved before moving forward. • An additional in vivo proof-of-concept study should be considered before initiating the proposed translational studies. • The acute rat efficacy study should establish the equivalency of groups prior to treatment and it is unclear whether the different doses are really meaningful. • It is unclear what the AAV5:GFP chronic rat study will tell them and why the product itself is not used. • The mini pig studies seem premature. The optimization of vectors, dosing, timing of dosing, and repeat dosing should be done first in mice and/or rats. • Why test different routes of administration, but do a mini pig safety and dose finding with injections? It is unclear why some of these studies are not combined. • The safety studies should not be done without guidance from the FDA. Continuous ECG monitoring and blood testing should be done at minimum. • The order of proposed tasks does not present a clear path towards an IND with appropriate regulatory engagement.
GWG Votes	**Is the proposal feasible?**
Yes: 9	• The proposal suffers from an unclear rationale for candidate selection and a lack of compelling in vivo data supporting the mechanism of action.
No: 6	• The project lacks focus and should be re-worked to make sure the necessary studies are done in the right order. • The proposed therapy is a great idea but premature at this point.

Application #	TRAN1-11611
Title (as written by the applicant)	Development of a human stem cell-derived inhibitory neuron therapeutic for the treatment of chronic focal epilepsy
Translational Candidate (as written by the applicant)	A cellular therapeutic comprised of inhibitory nerve cells produced from human stem cells
Area of Impact (as written by the applicant)	Drug-resistant chronic temporal lobe epilepsy
Mechanism of Action (as written by the applicant)	The product candidate is intended to be delivered into the seizure focus, integrate, and secrete the inhibitory neurotransmitter GABA to rebalance neural electrical activity in the brain and eliminate/reduce seizures.
Unmet Medical Need (as written by the applicant)	The seizures in approximately one-third of epilepsy patients do not adequately respond to current anti-epileptic drugs. Alternative surgical interventions are highly invasive and damage brain tissues. The proposed product candidate is intended to be restorative and long-acting.
Project Objective (as written by the applicant)	Pre-IND meeting; Pilot material manufactured
Major Proposed Activities (as written by the applicant)	• Finalize manufacturing process to be appropriate for future clinical use • Produce Pilot product using the intended process, confirm efficacy in two rodent models of chronic epilepsy and demonstrate safety at maximum dose • Select intended clinical cell delivery device and conduct pre-IND meeting to confirm IND-enabling preclinical requirements
Statement of Benefit to California (as written by the applicant)	Epilepsy is the fourth most common neurological disorder affecting more than 400,000 people in the State of California. One-third of epilepsy patients are considered to be drug-resistant and have persistent, uncontrolled seizures that can be disabling and affect quality of life. Alternative surgical interventions are highly invasive and may cause lasting impairment. This proposal aims to further develop a cellular therapeutic for treating drug-resistant epilepsy.
Funds Requested	$5,246,287
GWG Recommendation	***(1-84): Not recommended for funding***

SCORING DATA

Final Score: 78

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

Mean	76
Median	78
Standard Deviation	6
Highest	84
Lowest	60
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?

Yes: 14	• Temporal lobe epilepsy is an important need, and it is good to see someone working on a solution in this area. However, there is lack of clarity around the patient benefit and the true clinical goal. • The concept of inhibitory interneurons in this space is a good one, and has potential applications in other areas such as chronic pain. While it may be a difficult path to translation for this product, this project may assist in developing stem cell technologies outside of refractory epilepsy. • The treatment is likely to be economically valuable.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 10	• The plan and proposal to use inhibitory neurons makes sense. • Many of the current surgical procedures have only a 50-60% long-term efficacy. Current advanced imaging shows that these seizures are more complex than one small area. It is unclear how the proposed treatment at a single site would be better than the current procedure. • A possible MRI compatible device for delivery is proposed. However, conventional stereotaxis is extremely accurate and seems unnecessary. The volume and rate of delivery are more important considerations for possible tissue damage.
No: 5	• The target reduction of seizures they are aiming for seems small, and may be easier to achieve in the animal models than in humans.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 3	*none*
No: 12	• The proposed animal models don't use medications as controls as they would be used in the clinic. It is unclear if this is because the animal models don't have a response to medications or not. Even if they do not, this may be a missed opportunity to see an effect, ie. changing treatment-resistant to treatment-sensitive. • The cell derivation and sorting process with proprietary antibodies is complex and adds risk to the project. • Manufacturing aspects were difficult to assess as very few manufacturing details were provided. We tried very hard to get details on the CMC section but the applicants were not forthcoming.
GWG Votes	**Is the proposal feasible?**
Yes: 9	• There were challenges in evaluating the feasibility of CMC/manufacturing based on the information provided. • The team seems good, engaging several CROs.
No: 6	• The applicant will be dependent on CROs to meet the timelines. • Feasibility was unclear because of the lack of details in the application.

Application #	TRAN1-11571
Title (as written by the applicant)	Pre-clinical development of a small molecule therapeutic for the systemic treatment of osteoarthritis
Translational Candidate (as written by the applicant)	A novel small molecule drug candidate, CX-011
Area of Impact (as written by the applicant)	CX-011 will be targeted to prevent the advancement of, or reverse, osteoarthritis (OA)
Mechanism of Action (as written by the applicant)	CX-011 protects a patient's own cartilage stem/progenitor cells, shielding them from signals that would overstimulate them and cause them to degrade the cartilage around them. Because of this, CX-011 may interrupt the disease cycle and allow cartilage stem/progenitor cells to repair cartilage damage. These changes in the joint should reduce pain and increase mobility in treated patients.
Unmet Medical Need (as written by the applicant)	25 million adults suffer from osteoarthritis. Beyond reducing pain, there are no current treatments that slow or stop the progression of osteoarthritis. CX-011 could become the new standard of care by slowing or reversing OA, positively impacting the lives of millions of adults.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Rodent studies to optimize dosage amount and formulation • Toxicity studies in rodents and dogs to verify safety of the drug • Testing dosages of CX-011 in a dog model of OA immediately and some time after injury to assess efficacy in FDA-required large animals
Statement of Benefit to California (as written by the applicant)	5.9 million Californians suffer from arthritis. Currently, treatments for osteoarthritis focus on pain management, only treating the symptoms of the disease. CX-011 protects cartilage stem/progenitor cells, making them resistant to degenerative signals and potentially helping them repair cartilage damage. Therefore, CX-011 could be the first treatment to interrupt the disease cycle in OA, potentially changing the lives of millions of Californians by reducing pain and increasing mobility.
Funds Requested	$2,736,500
GWG Recommendation	***(1-84): Not recommended for funding***

SCORING DATA

Final Score: 70

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

Mean	70
Median	70
Standard Deviation	8
Highest	80
Lowest	50
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 11	• The potential impact is tremendous given the burden of disease in OA. • OA has a large cost to society and quality of life. While hip and knee replacement surgery has been deemed one of the most cost-effective procedures in the history of medicine, preventing or reversing its effects would serve patients tremendously. • It was important that the investigators characterized the potential for CX-011 and its major metabolite to drive the proliferation of tumor cells.
No: 4	• The stem cell component of this application is weak.
GWG Votes	**Is the rationale sound?**
Yes: 9	• The rationale is sound given the treatment paradigm. • The preliminary data is supportive. • The mechanism of the proposed therapeutic is novel and could have a significant impact on the disease.
No: 6	• There is concern about Fig. 14, where the sham looks better than the active agent. I don't see sufficient preclinical support to warrant moving forward.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 7	• There is good experimental design, testing doses and timing of doses at various time points in the disease.
No: 8	• Although the research group has hired a toxicologist consultant, the preclinical plan needs to be optimized. Some standard development tasks are missing (e.g. understanding exposure in different species before proceeding to additional PK/toxicity studies). ○ Characterization of the in vitro metabolism of CX-011 in the human, rat, dog and large animal models is needed. ○ Salt selection should occur before conducting in vivo studies. ○ In vivo PK should be evaluated in the rat, dog, and possibly large animal models. ○ Pilot toxicology experiments should be conducted in the rat and appropriate large animal species (14 days in rat and a dose range finding study in large animal species). ○ An in vitro pharmacology selectivity panel should also be conducted. ○ In vitro genotoxicity evaluations should be conducted prior to the pre-IND meeting. • Studies not needed for the pre-IND meeting include: ○ Definitive human P450 inhibition studies are not needed, though a screen is. ○ It is recommended that pilot toxicology studies are not turned into pharmacology studies.
GWG Votes	**Is the proposal feasible?**
Yes: 9	• There are still significant concerns regarding the safety profile, and also regarding the timeline. • There are concerns about the oral treatment/availability of this agent and how the prior work was done. Is the sham better? • With a properly designed program, this approach could have a significant impact on patients.
No: 6	• Aggressive timeline. • The timeline appears impossible.

Application #	TRAN1-11617
Title (as written by the applicant)	Small molecule PTP-Sigma inhibitor for human hematopoietic regeneration
Translational Candidate (as written by the applicant)	DJ009 is a small molecule inhibitor of PTP-Sigma that acts on hematopoietic stem and progenitor cells.
Area of Impact (as written by the applicant)	Severe neutropenia in patients receiving chemotherapy and graft failure and neutropenia in patients undergoing cord blood transplantation.
Mechanism of Action (as written by the applicant)	DJ009 inhibits a receptor tyrosine phosphatase, PTP-S, that is expressed on human hematopoietic stem cells via allosteric inhibition. Via inhibition of PTP-S, DJ009 promotes activation of RAC1, which, in turn, induces expression of the pro-survival protein, BCL-XL, and the kinase, CDK2. These signals cause early regeneration of hematopoietic stem cells after myelosuppression, thereby promoting the accelerated recovery of white blood cells, neutrophils and stem cells.
Unmet Medical Need (as written by the applicant)	Thousands of patients receive myelosuppressive chemotherapy or hematopoietic cell transplantation in the treatment of cancer. Such treatments deplete blood counts, leading to hospitalizations and infections. DJ009 treatment accelerates recovery of blood counts, thereby reducing these morbidities.
Project Objective (as written by the applicant)	Begin pivotal IND-enabling pre-clinical studies
Major Proposed Activities (as written by the applicant)	• Pilot synthesis of DJ009 and process development - Synthesis scale-up, preparation and characterization of DJ009 - Production of GLP-grade DJ009 • Optimization of mouse models of hematopoietic recovery, NSG models -ADME and PK/PD studies, Toxicology -Completion of pre-clinical in vivo studies • Development of clinical trial protocol -Preparation of pre-IND information package -Conduct pre-IND meeting with FDA
Statement of Benefit to California (as written by the applicant)	This proposal will benefit the State of California in several ways: First, our therapeutic has the potential to improve outcomes and decrease hospitalizations for tens of thousands of Californians receiving chemotherapy or undergoing hematopoietic cell transplantation annually. Second, we have patented new composition of matter, a new class of small molecule drugs that promote human stem cell regeneration. Third, investment in our technology will generate new jobs and revenue for California.
Funds Requested	$2,787,909
GWG Recommendation	***(1-84): Not recommended for funding***

SCORING DATA

Final Score: 70

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

Mean	68
Median	70
Standard Deviation	7
Highest	84
Lowest	60
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 8	• There are already some available drugs and there are other similar products in development making good progress. It is unclear how this product really stands out. • The product, in theory, could shorten hospital duration and may decrease the incidence of infections in patients who have received myelosuppressive chemotherapy for cancer. A small molecule would likely be less expensive than the current biologic therapies. • The advantage of DJ009 over commercial GCSF should be explained in greater detail. • Mobilization of cells other than myeloid series could be advantageous. • As a small molecule, the drug might be better developed outside of CIRM funding.
No: 7	• If truly effective at inducing more rapid recovery without toxicity, then this product could be useful. • It is unclear if this will be superior to and replace the use of GCSF, so the potential impact and value proposition is unclear. • The preclinical data are less than compelling. • There is an unclear understanding of potential risks/toxicity of product (e.g., potential inadvertent protection of cancer stem cells).
GWG Votes	**Is the rationale sound?**
Yes: 6	• An analogous inhibitor was used in irradiated mice provides a proof of principle for this compound. The data is showing hints of effects, but the differences seem small.
No: 9	• There is limited data to support the efficacy and mechanism of action. • Based on the available data, the case for DJ009 being superior to GCSF is weak. • There are major concerns regarding the potential for on-target specificity but off-therapeutic toxicities. PTP-S is expressed at high levels in many other tissue types, which was not mentioned in the application. In other tissues, PTP-S associated with cancer development, nerve regeneration, autoimmune disease. • Concern regarding the potential for adverse response in cancer stem cells (enhanced self-renewal, reduced apoptosis). • Unclear how the proposed increase in HSC self-renewal can also lead to more rapid absolute neutrophil count recovery (impact on later amplifying progenitor populations).
GWG Votes	**Is the proposal well planned and designed?**
Yes: 4	• Metabolism evaluation in the large animal model as a contingency plan is not appropriate for safety evaluation.
No: 11	• The following should be investigated before moving forward with development of this treatment: ○ The impact of DJ009 on normal HSC behavior: Are mature WBCs and neutrophils also effected by DJ009? ○ Assessment of the potential protective effect of DJ009 on cancer stem cells, including post-chemotherapy ○ Toxicology on those tissue types that express high levels of PTP-S (e.g. brain, fat, ovary) ○ PTP-S in mice and humans is structurally different. It is unclear what the biological ramifications of these differences are. (e.g. Structural insights into the homology and differences between mouse protein tyrosine phosphatase-sigma and human protein tyrosine phosphatase-sigma. Hou L1, Wang J, Zhou Y, Li J, Zang Y, Li J.) ○ What is the phosphatase selectivity profile of DJ0009? • Moving the pre-IND meeting with the FDA earlier in the project plan is recommended.
GWG Votes	**Is the proposal feasible?**
Yes: 8	• It is unclear whether the team has small molecule development experience. The team could benefit from an experienced nonclinical toxicologist and ADME scientist. • Production of the compound is feasible, as are the proposed toxicity studies.
No: 7	• Supporting data are limited and early effects are not very impressive.

Application #	TRAN1-11569
Title (as written by the applicant)	Lentiviral vector expression of Ube3a for the treatment of Angelman syndrome
Translational Candidate (as written by the applicant)	Our therapeutic candidate is human CD34+ hematopoietic stem cells genetically modified to overexpress human Ube3a via lentiviral vector transduction.
Area of Impact (as written by the applicant)	Currently, there is no cure for Angelman Syndrome (AS). Our therapeutic candidate has the potential to offer a treatment for patients affected by AS.
Mechanism of Action (as written by the applicant)	By performing an autologous hematopoietic stem cell transplant with the Ube3a lentiviral vector gene modified cells, patients will receive an immune system which overexpresses the modified form of human Ube3a. The gene modified immune system, which will circulate throughout the body, will secrete and deliver Ube3a to affected cells thus correcting the AS phenotype.
Unmet Medical Need (as written by the applicant)	Currently, there is no cure or effective treatment for AS. Our therapeutic candidate has the potential to offer a one-time treatment for patients affected by AS.
Project Objective (as written by the applicant)	We will hold a pre-IND meeting with the FDA.
Major Proposed Activities (as written by the applicant)	• Produce GMP-equivalent Ube3a lentiviral vectors and evaluate their safety and functionality in human CD34+ hematopoietic stem cells. • Evaluate the in vivo efficacy of the Ube3a vector transduced human CD34+ cells in a humanized mouse model of Angelman Syndrome. • Evaluate the safety and toxicity of Ube3a vector transduced human CD34+ cells in a humanized AS mouse model.
Statement of Benefit to California (as written by the applicant)	Angelman Syndrome currently has no cure or effective treatment strategy. With an incidence rate of 1/12,000 births with further cases undiagnosed, there is a need for new treatment strategies to be developed for these patients. Our strategy, if successful, would allow for a one-time and life long treatment that would allow for patients to be more independent and potentially self-sufficient for the rest of their lives.
Funds Requested	$2,400,107
GWG Recommendation	***(1-84): Not recommended for funding***

SCORING DATA

Final Score: 70

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

Mean	66
Median	70
Standard Deviation	8
Highest	75
Lowest	50
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 11	• Angelman Syndrome is a rare neuro-developmental disorder. There is no corrective therapy or therapeutic compound approved for this genetic disorder. • If the proposed cell therapy were successful, it would have a significant impact on this unmet medical need and may provide information to guide similar therapies. However, at this early stage of developmental testing, it is difficult to assess the actual likelihood of success or impact.
No: 4	• The rationale for bone marrow transplantation seems poor without a cross-correction mechanism for this disease. • A great deal of the appropriate experimentation has not been conducted. In particular, there is no demonstration of cross-correction or enzyme delivery, and the necessary control of transducing HSCs with an empty vector is missing. Thus, although the behavioral data is intriguing, the project is too early for this type of funding.
GWG Votes	**Is the rationale sound?**
Yes: 2	*none*
No: 13	• The preliminary data is interesting but needs additional proof of efficacy. More support for the concept of cross-correction in this disease is needed. The demonstration of enzymatic correction in mutant cells is essential. • The preclinical data lacked critical controls: mice treated with stem cells transduced with an empty vector. • Quantification of engraftment is also needed. • It is necessary to know if this treatment has to be done pre-symptomatically to obtain benefit.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 6	• Good animal model data. • It is unclear why while Milestone 2 experiments utilize the 6-8 week mouse intravenous delivery model (which presumably reflects the likely IND/clinical trial design), while Milestone 3 safety studies revert back to the prior newborn transplant model.
No: 9	• Some controls seem lacking in the animal work. The appropriate control for these experiments would be GFP expressing lentivirus to transduce human CD34+ cells. An empty cassette or a GFP cassette control is highly recommended.
GWG Votes	**Is the proposal feasible?**
Yes: 10	• This is a good team with the necessary resources in place. • There does not seem to be any integration analysis which is common when evaluating the safety of lentiviral vectors.
No: 5	• Until appropriate controls are done it is difficult to tell if the project is feasible. More preliminary data is needed.

Application #	TRAN1-11572
Title (as written by the applicant)	Cross-correction of MPSI by lentiviral vector expression of human IDUA in autologous hematopoietic stem cells
Translational Candidate (as written by the applicant)	Our therapeutic candidate is human CD34+ hematopoietic stem cells genetically modified to overexpress human IDUA via lentiviral vector transduction.
Area of Impact (as written by the applicant)	Currently, there is no cure for MPSI. Our therapeutic candidate has the potential to offer a treatment for patients affected by MPSI.
Mechanism of Action (as written by the applicant)	By performing an autologous hematopoietic stem cell transplant with the IDUA lentiviral vector gene modified cells, patients will receive an immune system which overexpresses the wild type form of human IDUA. The gene modified immune system, which will circulate throughout the body, will secrete and deliver wild type IDUA to affected cells thus correcting the MPSI phenotype.
Unmet Medical Need (as written by the applicant)	Currently, there is no cure or effective treatment for MPSI. Our therapeutic candidate has the potential to offer a one-time treatment for patients affected by MPSI.
Project Objective (as written by the applicant)	We will conduct a pre-IND meeting with the FDA.
Major Proposed Activities (as written by the applicant)	• Produce GMP-equivalent IDUA lentiviral vectors and evaluate their safety and functionality in human CD34+ hematopoietic stem cells. • Evaluate the in vivo efficacy of the hIDUA vector transduced human CD34+ cells in a humanized mouse model of MPSI. • Evaluate the safety and toxicity of hIDUA vector transduced human CD34+ cells in a humanized NRG mouse model.
Statement of Benefit to California (as written by the applicant)	Lysosomal storage diseases, including MPSI, are genetic diseases that affect the CNS and other major organs. Currently, there is no cure for MPSI and palliative care only marginally improves patient's lives. Enzyme replacement therapy is available, however, this approach does not effectively enter the CNS. By using the immune system to deliver wild type IDUA systemically, affected cells would uptake the proteins thus providing an effective treatment and potential cure for patients.
Funds Requested	$1,615,643
GWG Recommendation	***(1-84): Not recommended for funding***

SCORING DATA

Final Score: 65

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

Mean	61
Median	65
Standard Deviation	6
Highest	65
Lowest	50
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 8	• Mucopolysaccharidosis Type I (MPSI) is a lysosomal storage disease caused by a deficiency in IDUA protein activity. Bone marrow transplant or cord blood transplant has been available for MPSI for over 2 decades. Enzyme replacement therapy has been available for MPSI since 2004. Therefore, for this product to ultimately be successful, it will have to demonstrate superiority over these two interventions, which will likely be very difficult clinically (as experienced by other industrial investigations in the same disease). • The product would accelerate the likelihood of successfully developing stem cell technology that could significantly improve patient care, but the hurdles are several. One is the production of very high amounts of enzyme superior to allotransplant and second would be achieving excellent engraftment long-term with minimal conditioning.
No: 6	• Currently the standard of care is bone marrow transplant, but it is not a perfect solution. • As this is a severe and untreatable disease, combining gene therapy with autologous HSCs would - if successful - be transformative for patients.
GWG Votes	**Is the rationale sound?**
Yes: 3	*none*
No: 11	• The applicants provide convincing data for the ability to produce the missing enzyme, and further demonstrate that there are no adverse effects on colony forming CD34 positive HSCs. They also demonstrate phenotypically normal macrophages. Most importantly, in a mouse model of the disease, there are benefits of this proposed therapy on behavior, on bone growth, and on spleen size. Despite the above positives, there is no demonstration of enzyme delivery to the brain. • There's no indication of what the engraftment was. The transplant data were also performed with mice that were 2-5 days old by intra-hepatic transplant which has no clinical correlate and which is quite contrived.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 0	*none*
No: 14	• The investigators want to move from transplanting neonatal mice into transplanting mice 3 months/12 weeks of age. They hope to reverse the phenotype though they do not demonstrate that such a phenotype exists at this stage, so it is unclear if there is anything to halt or reverse. • The authors plan on performing transplantation experiments with busulfan conditioning though there's no data presented about engraftment levels. They suggest routine engraftment between 38-65% but do not show data. Secondarily, they consider success to be 25% engraftment in human cells though the rationale for choosing this number is unclear. • The authors suggest that a control group is BRG IDUA deficient mice transplanted with un-transduced human CD34+ cells. I suggest the authors actually transduce the cells with the GFP or empty cassette virus. The virus may integrate with any of the regions in CD34+ genomes and cause activation of pathways that could trigger a compensatory effect to lessen the MPS1 phenotype when the mice are transplanted, thereby delivering results that show the effect based on just antiviral integration into an active region. • There are many differences between sources of cells, routes of administration and age of animals in the proposed experiments that are not explained.
GWG Votes	**Is the proposal feasible?**
Yes: 7	• The team appears qualified and it appears they have the staff and expertise to run the experiments, but it is not clear if an MPSI expert is on the team.
No: 7	• The proposed milestones include manufacturing GMP clinically equivalent lentiviral vectors. Given the facility, it is unclear why GMP produced lentiviral vectors are not used. It seems the pilot data was also using GMP equivalent lentiviral vectors so milestone one seems redundant with what has been previously done. • The team is outstanding in some respects, but notable for the lack of an MPSI expert. • Potential risks and their mitigation are not well addressed.

Application #	TRAN1-11545
Title (as written by the applicant)	A Novel Drug for Human Pancreatic Cancer Stem Cell Eradication
Translational Candidate (as written by the applicant)	DC-1, a stable non-toxic small molecule that has shown widespread utility in pre-clinical tests for cancer stem cells.
Area of Impact (as written by the applicant)	Pancreatic Cancer
Mechanism of Action (as written by the applicant)	DC-1 is a small molecule that kills human pancreatic cancer stem cells (hPCSCs) by selectively targeting drug-resistant secondary spheroids. Normal, healthy, non-dividing cells are not touched. Aggressive, highly dividing hPCSCs are selectively killed. DC-1 is the only known small molecule that induces apoptosis and inhibits autophagy in pancreatic cancer. It acts by inhibiting key, important over-arching molecular pathways in hPCSCs.
Unmet Medical Need (as written by the applicant)	Pancreatic cancer is currently a major cancer increasing in incidence in the U.S. (almost 6,000/yr Californians diagnosed) and is an unmet medical need.
Project Objective (as written by the applicant)	Pre-IND Summary and Pre-IND Meeting
Major Proposed Activities (as written by the applicant)	• GMP Synthesis of the drug candidate • Efficacy testing of the drug candidate • Safety testing of the drug candidate
Statement of Benefit to California (as written by the applicant)	In California, 6,000/year are diagnosed with pancreatic cancer (PC). PC is increasing. PC is the 3rd most common cause of mortality due to cancer, and soon it will be 2nd. PC in California costs almost $1 billion annually. PC patients are often resistant to clinical therapies. Drugs to treat PC are ineffective and the only treatment is surgical resection. Front-line chemotherapies cause serious side effects. Thus, PC remains a major unmet medical need. DC-1 will address the need for a new PC medication.
Funds Requested	$3,939,730
GWG Recommendation	***(1-84): Not recommended for funding***

SCORING DATA

Final Score: --

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

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

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 10	• There are currently no drugs that target cancer stem cells, and any agent to target cancer stem cells would be important and fiscally advantageous.

	• The development of treatments for pancreatic cancer is important for an expanding patient population.
No: 5	• The program looks like it could benefit patients who have developed resistance to other therapies. However, the potential impact is not clear based on the existing data, especially if the new therapy must be administered with other current therapies.
GWG Votes	**Is the rationale sound?**
Yes: 0	*none*
No: 15	• There is insufficient data supporting the mechanism of action and specificity of the proposed therapy. • The specific mechanism of action for the agent and how it targets CSCs is not clear. • The link between this drug candidate and targeting of cancer stem cells is not clear. While cancer stem cells may be important in pancreatic cancer, the application makes a big leap in claiming that this product targets stem cells. They show that this drug acts on a single cell line with avb3 integrin overexpression. However, there is weak evidence that avb3 integrin overexpression is a marker of cancer stem cells, and that targeting this pathway will reduce the 'stemness' of tumors. • The drug is supposed to be specific for pancreatic cancer stem cells, but efficacy experiments were conducted in cell lines (breast, colon, etc) that do not appear to contain stem cells. This contradicts the proposed rationale for this product.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 1	*none*
No: 14	• There is not a clear development path towards a pre-IND meeting or IND. Some proposed studies are not necessary for a pre-IND meeting, while others would typically be completed after the meeting. Areas that need improvement include: ○ More preliminary data in other cells lines is needed. ○ It is not clear how they are going to formulate the therapy into an oral drug. ○ An understanding of the metabolism across the human, rat, dog, and large animal models of DC-1 is required. ○ Studies utilizing radiolabeled material are not necessary at this time. Likewise, biodistribution studies are not required at this time. ○ Both rat and non-rodent pilot toxicology studies will be needed for a robust pre-IND meeting with the FDA. ○ A pivotal 28-day rat safety assessment study should be conducted after the pre-IND meeting. ○ A draft protocol and supporting pilot nonclinical data (toxicology and ADME) will help in gaining agreement from the FDA on the final design of the preclinical safety assessment studies. ○ As DC-1 will be used in conjunction with cytotoxic agents, it is unclear if the evaluation of genotoxicity beyond pilot studies will be needed.
GWG Votes	**Is the proposal feasible?**
Yes: 7	• The team appears capable of carrying out these studies. • The program would benefit from an experienced toxicologist and drug metabolism/pharmacokinetics scientist to help address the design of the necessary studies.
No: 8	• Performing the proposed studies is feasible but will not guide this program appropriately to a successful pre-IND meeting. For example, there is no mention of pharmacokinetic studies to guide other nonclinical studies and clinical planning. • The application assumes it will be easy to dose this drug orally, but with limited evidence (4 rodents dosed orally). Formulating this drug candidate into an oral therapy could take significant work that is not addressed in this proposal.

Application #	TRAN1-11616
Title (as written by the applicant)	Human Gingival Mesenchymal Stem Cell-based Treatment of Peri-implantitis
Translational Candidate (as written by the applicant)	Autologous stem cells from the gingiva that can adhere to moist oral tissues when added to a hydrogel
Area of Impact (as written by the applicant)	Peri-implantitis (PI), a destructive inflammatory process around dental implants in function, leading to pocket formation and loss of supporting bone
Mechanism of Action (as written by the applicant)	Autologous gingival mesenchymal stem cells (GMSCs) that are isolated from discarded gingival tissues with anti-inflammatory and anti-bacterial properties that undergo osteogenic differentiation when encapsulated in an adhesive hydrogel loaded will be administered into inflamed peri-implantitis bone defects. Peri-implantitis (PI) includes bleeding, suppuration, and attachment loss clinically, and bone loss radiographically, which can be evaluated non-invasively before and after candidate cell-based therapy.
Unmet Medical Need (as written by the applicant)	PI prevalence in up to 56% of patients often leads to implant loss and the need for major reconstruction. Currently, no therapies exist to regenerate bone around implants. Cell-based therapies with osteogenic capabilities are a huge unmet need with major market and immediate clinical applications.
Project Objective (as written by the applicant)	Pre-IND meeting and finalization of GMP processes
Major Proposed Activities (as written by the applicant)	• Development of GMP processes and procedures to culture and expand gingival mesenchymal stem cells to prepare for clinical trials • Quality control and quality assurance for reproducibility in mechanical properties, cell viability, storage, and sterility under GMP conditions • Evaluation of clinical, radiographic, and histologic parameters of peri-implant bone regeneration after GMSC-based therapy
Statement of Benefit to California (as written by the applicant)	Peri-implantitis is a destructive inflammatory process around osseointegrated implants, leading to pocket formation and supporting bone loss, often resulting in implant failure. With 5 million implants placed annually, and a conservative estimate of 10% PI , that is 500,000 new cases annually. Utilizing our optimized GMSC-based therapeutic encapsulated in an adhesive hydrogel to regenerate bone around ailing implants, millions of Californians with these devastating dental problems will benefit.
Funds Requested	$3,927,007
GWG Recommendation	***(1-84): Not recommended for funding***

SCORING DATA

Final Score: --

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

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

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in

the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 3	• There are other methods to address peri-implantitis, but this may be a better solution. I'm not sure of the value proposition.
No: 11	• Innovative approach for replacing bone loss but the incidence of the disease is not clearly stated. • The applicants did not make a strong case for the specific unmet medical need addressed by this therapy. The antibacterial potential of these cells is no where near the efficacy of antibiotics, which would always be first line. While there are challenges treating peri-implantitis, there are bone void fill products available and how these GMSCs would offer a better cost-benefit was not presented. • The value proposition is low in the proposed patient population and indication. Dentistry is mostly self-pay and patients will be reluctant to pay for an expensive therapy that might prevent problems in the future.
GWG Votes	**Is the rationale sound?**
Yes: 4	• Rationale is sound. It is unclear why allogeneic MSC are not to be used as this would be technically simpler and could provide more rapid access to treatment. There is also poorer response using gingival versus bone marrow-derived MSC.
No: 10	• MSCs have been shown to produce bone and potentially some ability to fight infections (although antibiotics are cheap and effective) as well as some anti-inflammatory properties. • Unclear rationale for an autologous-based approach. • It is unclear why human gingival stem cells were selected over the more effective bone marrow-derived MSCs. • The methods and preparation of the autologous cell isolation is not clearly explained. • The preliminary data is pretty thin. The bone repair is pretty small and in an easy model in the studies presented here. • It was hard to follow the proposal as some of the figures don't have legends.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 2	• Earlier contact with the FDA is recommended to discuss pre-clinical data studies and hydrogel sterilization. Additional regulatory support may be needed.
No: 12	• Additional biodistribution, pharmacokinetic or pharmacology are likely needed, but not mentioned. Applicants need to engage some help here.
GWG Votes	**Is the proposal feasible?**
Yes: 6	• Timelines and goals should be achievable. • There are no financial resources to support mitigation strategies.
No: 8	• There are clear risks but not much offered in the way of mitigation. Additional financial plans to support additional studies seem to be lacking.

Application #	TRAN1-11596
Title (as written by the applicant)	RIA-derived skeletal stem and progenitor cells for bone repair
Translational Candidate (as written by the applicant)	Autologous bone/bone marrow derived skeletal stem and progenitor cells (SSPCs)
Area of Impact (as written by the applicant)	Non-union bone fractures
Mechanism of Action (as written by the applicant)	The cells will differentiate into the missing osteoblasts, contributing to repair the bone (cell replacement).
Unmet Medical Need (as written by the applicant)	In the setting of high energy trauma with significant local tissue damage or in systemically compromised hosts, bone fractures often can't heal by themselves. Patients' bone can be surgically bridged, but replacement and healing of the missing bone fragment is often extremely challenging.
Project Objective (as written by the applicant)	Pre-IND meeting to advance toward its clinical use
Major Proposed Activities (as written by the applicant)	• Optimize isolation of SSPCs (to achieve maximum yields) and determine how long the cells can be stored without losing efficacy. • Define a minimal effective dose, determine the best route of delivery, and thoroughly characterize the product. • Perform pilot safety studies on persistence and distribution and complete regulatory work for a pre-IND meeting with the FDA.
Statement of Benefit to California (as written by the applicant)	Bone fractures are quite common. From these, about 10% will be very challenging to heal, due to the amount of tissue loss or the patient's background (old age, with diabetes, etc.). The development of this therapy will directly benefit citizens in California, as they will have the opportunity to receive this novel stem cell therapy to promote bone repair.
Funds Requested	$1,340,057
GWG Recommendation	***(1-84): Not recommended for funding***

SCORING DATA

Final Score: --

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

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

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 1	*none*

No: 14	• There are other therapies available and this one doesn't appear to add anything which would be better than the current methods. • There is extremely limited proof-of-concept and supporting data for the proposed therapeutic approach. • The impact is unclear given the type of surgery.
GWG Votes	**Is the rationale sound?**
Yes: 0	*none*
No: 15	• The rationale is unclear. Industry may be a better partner than CIRM. • The mouse studies with n=4 show increased mineralization, but not really increased or improved healing. The product was only tested against control, not tested against other drugs/methods. • The mouse tests were also only done using a single RIA effluent, so it is unclear whether the product will be widely useable. • It was also unclear what the differences in the product would be from patient to patient.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 0	*none*
No: 15	• The proposal is poorly organized and planned. • The applicants are devising a method to avoid blood clots and deplete red blood cells, and only testing one concentration of heparin. They will count the product to see if they get higher cell yields, but not checking if this affects the cells in any way. They also propose separation of red blood cells with Ficoll, which seems cumbersome and prone to contamination. • The rat studies are likely a better model, but it is not clear if the dosing in the rat model will in any way mimic the clinical route. In rat studies they put the product in the matrigel but not IV or percutaneous injection. It would appear they don't know what the clinical route of delivery will be. Large animal studies will be needed at some point. • In another study they plan to test the route of delivery - IV vs percutaneous, only checking to see where the cells home to, but not checking to see if it alters healing or if one works better than the other. It doesn't appear they will test timing or dose response here. It is not clear if they understand what the clinical route will be.
GWG Votes	**Is the proposal feasible?**
Yes: 0	*none*
No: 15	• The proposal offers little insight in terms of a goal in its current form. A pre-meeting with the FDA may be helpful for the group. • The proposal was confusing. • Clinicians are needed on the proposal to consider the endgame.