APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Resubmission	Previous CIRM Funding	Disease Indication	Product Type	Approach
TRAN4-14124	Cell Villages and Clinical Trial in a Dish with Pooled iPSC-CMs for Drug Discovery	**$1,350,000**	**Y**	**90**	90	10	60	98	13	1	N	N	Cardiovascular disease	Tool	A screening tool composed of a pooled set of iPSC-derived cardiomyocytes to screen for drug candidates
TRAN1-14003	Specific Targeting Hypoxia Metastatic Breast Tumor with Allogeneic Off-the-Shelf Anti-EGFR CAR NK Cells Expressing an ODD domain of HIF-1α	**$6,036,002**	**Y**	**87**	87	3	82	95	12	2	N	N	Metastatic breast cancer	Cell therapy	Development of a CAR-Natural Killer Cell therapy that targets breast cancer cells in tumor hypoxic environment
TRAN1-13983	CRISPR/Cas9-mediated gene editing of Hematopoietic stem and progenitor cells for Friedreich's ataxia	**$4,846,579**	**Y**	**87**	86	5	70	91	13	1	N	N	Friedreich's ataxia	Cell and gene therapy	An autologous therapy of genetically modified HSC to deliver functional frataxin to tissues in FA patients
TRAN1-13997	Development of a Gene Therapy for the Treatment of Pitt Hopkins Syndrome (PHS) - Translating from Animal Proof of Concept to Support Pre-IND Meeting	**$4,000,000**	**Y**	**85**	84	2	78	87	7	7	N	N	Pitt Hopkins Syndrome	Gene therapy	A gene therapy that restores expression of the TCF4 gene in neurons
TRAN1-13996	Overcoming resistance to standard CD19-targeted CAR T using a novel triple antigen targeted vector	**$4,168,679**	**N**	**83**	83	5	75	95	6*	7	Y	N			
TRAN1-13986	Adenine Base Editing for Autologous Hematopoietic Stem Cell Gene Therapy of CD3δ SCID	**$5,587,234**	**N**	**75**	76	8	65	90	4	11	N	N			
TRAN3-14001	Spinal subpial injection system for delivery of gene-based therapies in humans.	**$2,665,262**	**N**	**75**	76	5	70	85	3	12	N	N			
TRAN1-13976	Autologous Hematopoietic Stem Cell Gene Therapy for Sickle Cell Disease Using a Novel High-Titer, Bifunctional Lentiviral Vector	**$5,537,334**	**N**	**75**	76	5	70	85	1	13	N	Y			
TRAN1-14018	The First Orally Delivered Cell Therapy for the Treatment of Inflammatory Bowel Disease	**$1,822,685**	**N**	**70**	71	6	62	84	0	13	N	Y			
TRAN1-14022	Cone progenitor cells for prevention and treatment of retinal degeneration	**$4,037,829**	**N**	**70**	71	4	65	75	0	14	Y	N			
TRAN3-14004	Clinical translation of MPI for cellular imaging of CAR T cells	**$1,984,740**	**N**	**70**	68	3	60	70	0	14	N	N			
TRAN4-14015	Improving HSC and PBMC Fraction Quality by Enhancing Cord Blood and Leukopak Storage Using Novel Cryoprotectants	**$1,253,330**	**N**	**70**	68	7	55	80	0	15	N	Y			
TRAN1-14017	Gene Therapy for Alzheimer's Disease	**$2,827,578**	**N**	**-**	**-**	**-**	**-**	**-**	0	15	N	N			
TRAN3-14026	Optimizing Cell Therapy Delivery: Developing a Novel Device Designed to Protect Cells During Infusion	**$685,267**	**N**	**-**	**-**	**-**	**-**	**-**	0	15	N	N			

* Qualify for Minority Report

Application #	TRAN4-14124
Title (as written by the applicant)	Cell Villages and Clinical Trial in a Dish with Pooled iPSC-CMs for Drug Discovery
Translational Candidate (as written by the applicant)	Human stem cells in a dish engineered into heart cells to supplement, refine, reduce, and/or ultimately replace human clinical trials.
Area of Impact (as written by the applicant)	Increase genetic diversity of preclinical studies in human samples to de-risk clinical trials and save time and costs.
Mechanism of Action (as written by the applicant)	We will have several non-invasive human-derived stem cells collected and engineered into heart cells that replicate the patient's heart function. This collection of human-relevant heart cells can then be used for testing new drugs for preclinical studies prior to experimenting safety and efficacy on humans in clinical trials.
Unmet Medical Need (as written by the applicant)	Drugs often fail clinical trials due to insufficient safety or efficacy, with the former carrying substantial risk to patients. Our tool increases genetic diversity of human cell lines the drug can be tested on to better predict safety and efficacy in humans.
Project Objective (as written by the applicant)	Readiness for transfer to manufacturing.
Major Proposed Activities (as written by the applicant)	• Generate cell villages that models a collection of many diverse human hearts from different ethnic and genetic backgrounds. • Evaluate the response of cells with the treatment of doxorubicin, a chemotherapy, which has been shown to have variable cardiotoxicity. • Identify cell-specific and patient-specific response to doxorubicin from the cell village.
Statement of Benefit to California (as written by the applicant)	Cardiovascular diseases and cancer are the #1 and #2 leading causes of death in the US. This proposal aims to increase ethnic and genetic diversity representative of diverse populations such as California for evaluation of new drugs to supplement preclinical trials and better predict clinical trial outcomes.
Funds Requested	$1,350,000
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 90

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

Mean	90
Median	90
Standard Deviation	10
Highest	98
Lowest	60
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	1

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the 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 project have the necessary significance and potential for impact?
Yes: 13	• This is a platform technology based on the use of induced pluripotent stem cells (iPSC) lines. This technology has a good chance of accelerating drug development, making the process more efficient and less costly. • The proposal addresses an important unmet clinical need which is the ability to test a large number of iPSC derived lines from diverse patients at the same time. • If successful, this technology will provide a valuable tool to test the effect of drugs on cardiomyocytes (CMs) at this stage from several dozen different donors at the same time. • A bottleneck in drug testing is the variability of patient response to drugs. This project can address this issue by providing a well characterized and tested cells grouped together in what the investigators call "cell villages" where iPSC-CMs are cultured, differentiated, and tested together, then identified by matching to their single-cell profile. • Yes, the product can significantly enhance the delivery of personalized therapies for toxicity and efficacy testing. • The product, when commercially available, will provide researchers with the ability to examine the effect of drugs on several dozen patient-derived cell lines simultaneously. This significantly increases the confidence in identifying potential drug toxicity and variability in efficacy. • This is a high risk project but if it works, it will have a high impact in the field. • Although the potential for impact is overstated, I still found it to be a worthwhile project with potential to improve in vitro modeling. Also, I think anything that could reduce animal use, even to a small extent, is attractive. • It is hard to assess any impact on patient care and healthcare since it is a technology in early development and is not a therapeutic product. An indirect effect of this technology on patient care could be through the development of "better drugs", prevention of side effects, and the acceleration and increased efficiency of clinical trials overall.
No: 1	• I really struggle to understand the impact of this.
GWG Votes	**Is the rationale sound?**
Yes: 14	• This proposal aims to develop a "cell village" model that co-cultures and multiplexes different iPSC lines together that are then differentiated into cardiomyocytes (iPSC-CMs) for drug treatment, followed by single-cell analysis to demultiplex the cell village. • The scientific rationale is solid. It is based on the expanded potential for use of iPSC lines for disease modeling by replacing animal studies and testing drugs for toxicity and side effects. • The "cell village" idea is very novel and was never used before. The concept has multiple advantages over conventional in vitro and in vivo assays in drug development. It allows for mimicking a "clinical trial in the dish" by mixing cell lines from multiple individuals, accounting for multiple possible disparities between patients. • Data presented in the application support the further development of the "cell village" concept. • Data presented include significant expertise in iPSC-CM differentiation and assays, ability to identify drug toxicity parameters, demonstrated effects of doxorubicin on iPSC-CM, and ability to perform and analyze large datasets. • The technologies proposed in this application are already available and thus success is expected to be likely. • The data presented strongly support the proposal. Almost all the proposed assays and cell lines are already available to the team. • It is unclear how the "cell village" will work for cell and gene therapy products, where the immune system plays a huge role. If iPSC lines will be differentiated into immune cell types, alloreactivity should be addressed. Also, interactions of cells with the host immune system should be modeled. • The rationale is sound and attractive, but whether this platform will work and can be widely used as a product are open questions.

	• Given it is early development stage, it is unknown whether platform will work and can be widely used as a product. • The technology is all present. I just don't understand the impact.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 14	• The proposed outcome of the proposal will: (i) demonstrate the ability to demultiplex cell villages into single cells that can be correlated back to the parent iPSC line based on single-cell data with data from the patient, (ii) identify cell-specific and patient-specific response to treatment from the cell villages for clinical trial in a dish and drug discovery, (iii) provide disease-specific cell villages of iPSC-CMs for commercialization and distribution to private and public institutions, and (iv) enable the generation and characterization of additional disease-specific cell villages from the few thousand iPSC lines at the applicant institution as a future direction. • The cell villages will undergo functional cellular characterization and single-cell analysis to identify patient-specific and cell-specific aberrant changes to gene expression. Lastly, they will map expression to doxorubicin response, which will enable them to identify factors for stratifying patient populations in clinical trials and for drug discovery. • The data presented support the proposal and provide a high degree of confidence, especially given the history of collaboration between two key personnel. • Two key personnel are known for high-quality research involving cardiovascular disease modeling on iPS cell lines. • The proposal is very well written and flows logically. • Yes, the proposed milestones are to be completed in 24 months. • The project appears well planned. • The tools are state-of-the-art, but the proposal focuses on using the cell villages validating doxorubicin, which was published many years ago. • Some aspects were suboptimal, such as the use of duplicated figure (#12 and 17).
No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 13	• The milestones of the project are described in detail. The timeline is appropriate. The team is well-qualified. The company and academic investigator have a lot of experience with iPSC lines. • Yes, the proposed studies are well within the expertise of the research team. • Yes. The PI as well as the two co-founders have significant expertise in the studies proposed. • Considering the team, it is possible they will be able to complete the project within the timeline. • There is access to the cell lines and a close collaboration with the respective labs at a partner institution. • The cell lines and technologies are available to the team. • The contingency plan is well-outlined.
No: 1	• It doesn't seem likely there is going to be a licensed product at the end of this.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 14	• This is one of the most responsive applications in that regard. The design of the proposal inherently upholds the principles of diversity in that the cell lines that will be studied are from diverse patient backgrounds. • The biobank already has more than a few thousand iPSC lines, but the team suggests that they will be recruiting more donors as part of an outreach plan to enhance diversity. • Yes, the cell village product can be a valuable tool for researchers. • Table 1 provides an example of ethnically diverse iPSC lines readily available. • Excellent DEI section. • Strong DEI components.
No: 0	*none*

DIVERSITY, EQUITY, AND INCLUSION (DEI)

During the GWG discussion of the application, a GWG Board Member presented a critique and DEI score on whether the project upholds principles of diversity, equity and inclusion (DEI). DEI was discussed by the panel, and up to seven GWG Board Members provided final DEI scores and comments, shown in the table below. The responses were compiled and edited by CIRM for clarity.

DEI Score: 9.0

Up to 7 patient advocate and nurse 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.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	3	• 'Cell village' disease modeling using iPSC cultures could reduce current challenges to treatment in underserved communities. • Strong DEI components reflected in the application.
6-8: Responsive	1	*none*
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-14003
Title (as written by the applicant)	Specific Targeting Hypoxia Metastatic Breast Tumor with Allogeneic Off-the-Shelf Anti-EGFR CAR NK Cells Expressing an ODD domain of HIF-1α
Translational Candidate (as written by the applicant)	EGFR-CAR_sIL15 natural killer (NK) cells derived from CD34(+) umbilical cord blood hematopoietic stem cells (HSCs)
Area of Impact (as written by the applicant)	Patients with metastatic breast cancer, especially HER2-low breast cancer
Mechanism of Action (as written by the applicant)	EGFR-CAR_sIL15 natural killer (NK) cells are umbilical cord blood-derived CD34+ hematopoietic stem cells (HSCs) that are engineered to target EGFR and express soluble IL-15, and then differentiated into NK cells. To reduce potential off-target toxicity, the CAR is fused with the oxygen-dependent degradation domain (ODD) of HIF1a, leading to increased CAR expression within the low-oxygen tumor microenvironment. The CAR will not express or have limited expression in normal tissues, which have higher levels of oxygen.
Unmet Medical Need (as written by the applicant)	Breast cancer (BC) is the most common cancer and second leading cause of cancer death in women in North America. Successful translation of our safe, off-the-shelf cellular therapy of EGFR-CAR_sIL15 natural killer (NK) cells will diminish the life-threatening clinical manifestations of metastatic BC.
Project Objective (as written by the applicant)	Complete Pre-IND meeting and finalize IND plans
Major Proposed Activities (as written by the applicant)	• Manufacture EGFR-CAR_sIL15 NK cells and conduct PK/PD studies • Conduct pharmacology and toxicity studies • Efficacy testing of EGFR-CAR_sIL15 NK cells to optimize treatment schedule • Confirm efficacy of EGFR-CAR_sIL15 NK cells under optimized and safe conditions • Pre-IND meeting with FDA
Statement of Benefit to California (as written by the applicant)	In the United States, currently, breast cancer (BC) is the most common cancer, and it is the second leading cause of cancer death, including in California. While there has been a decline in BC deaths over the last 30 years, there is a persistent mortality gap between Black women and white women. Our goal is to develop an "off-the-shelf," ready-to-use cell therapy that is appropriate and easily accessible for any patient regardless of race, ethnicity, age, or socioeconomic status.
Funds Requested	$6,036,002
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 87

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

Mean	87
Median	87
Standard Deviation	3
Highest	95
Lowest	82
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	12

(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/RFA. Following the panel's discussion and scoring of the application, the 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 project have the necessary significance and potential for impact?
Yes: 14	• Triple-negative metastatic breast cancer represents an unmet medical need since there are no good treatment options available. If successful, the proposed product is likely to address this unmet need. • The product is based on the differentiation of NK cells from cord blood-derived hematopoietic stem/progenitor CD34+ cells. If trials are successful, the technology will significantly improve patient survival. • The advantage of the proposed CAR-NK product is in the vector design. It is novel and unique. The CAR-NK cells will be activated the most in hypoxic tumor tissue, which will prevent potential off-target, off-tumor toxicity. • Refractory triple negative breast cancer (TNBC) is a significant unmet need. While good statistics on recurrent disease are not available, estimates range from 20-30% of breast cancer overall. The median survival for metastatic TNBC is just over 13 months. • Yes there is potential, however the target product profile (TPP) did not provide a clear target dosing regimen. A product administered in a single infusion with durable effect would offer a greater value proposition than a product requiring multiple infusions. • An allogeneic approach that does not require donor-recipient matching is attractive. • Treatments for metastatic breast cancer are needed and off-the-shelf therapies may lead to more accessibility. • Metastatic breast cancer is an important disease and new therapies are needed.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• The proposal aims to translate an off-the-shelf allogeneic CAR-NK cell therapy for metastatic breast cancer. The NK cells are derived from cord-blood HSCs, which yields 50-fold more cells than cord-blood derived NK cells, and the team has adapted their current NK cell manufacturing platform to incorporate differentiation of NK cells from HSCs. • The scientific rationale is sound. The preliminary data presented in the application support further development. • Generally, yes. I'm not certain that switching off CAR in the absence of hypoxia is appropriate. Is it known that all breast metastases are hypoxic? • Overall, yes. However, the planned preclinical studies include a large number of timepoints suitable for a drug study, but not necessary for a cell therapy. For example, the PK/PD study (evaluating biodistribution) uses about 168 mice and has seven timepoints. The applicant will likely not be able to detect differences in biodistribution of EGFR-CAR_sIL15 NK cells between all seven timepoints. • The application suggests that these data will be used to set dosing, but they also state they have already targeted a dose. In actuality, the GLP toxicity studies would be needed to set the dosing. • If they plan to support multiple dosing in the planned clinical trial, their pre-IND enabling safety studies will need to include multiple doses. The value of the extensive preclinical work proposed here, at this stage, would in that case be limited.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 14	• Yes. The project plan is for CMC optimization, followed by biodistribution studies. The applicant will determine treatment dose, schedule, and efficacy in PDX model. • Generally, well planned and designed, but the large numbers of mice are not justifiable - especially the multiple time points/multiple mice in PK/PD studies. If multiple dosing is likely to be needed, the single dose studies are irrelevant.

	• Weakness 1: No information on EGFR expression (by tumor) threshold or the patient eligibility/inclusion criteria. • Weakness 2: No data to support selective activation of CAR in hypoxic tumor tissue. Are all tumors hypoxic compared to normal tissues? The applicant should provide a literature reference for this. • Weakness 3: Comparability between cord blood units should be included in the plan unless the team has concluded this study already. There is a mention of product consistency studies, but no information about results. • A caveat on the project plan is that it's unclear whether they are injecting human NK cells into C57BL6/J-hEGFR mice.
No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 14	• Complex manufacturing is noted, but there is a plan in place. • The milestones schedule looks good. The team is very well qualified to perform the work. • The preliminary data show feasibility of manufacturing the CAR NK cells, as well as preclinical efficacy. The cells are lytic in vivo in a B cell lymphoma and enhance survival in a metastatic breast cancer model.
No: 0	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 14	• Accessibility and affordability of the therapy are addressed in the DEI statement. • Adequate DEI Plan. • This proposed treatment is for a disease that disproportionally affects underserved populations.
No: 0	*none*

DIVERSITY, EQUITY, AND INCLUSION (DEI)

During the GWG discussion of the application, a GWG Board Member presented a critique and DEI score on whether the project upholds principles of diversity, equity and inclusion (DEI). DEI was discussed by the panel, and up to seven GWG Board Members provided final DEI scores and comments, shown in the table below. The responses were compiled and edited by CIRM for clarity.

DEI Score: 7

Up to 7 patient advocate and nurse 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.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	0	*none*
6-8: Responsive	3	• Adequate DEI Plan.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-13983
Title (as written by the applicant)	CRISPR/Cas9-mediated gene editing of Hematopoietic stem and progenitor cells for Friedreich's ataxia
Translational Candidate (as written by the applicant)	Autologous human CD34+ hematopoietic stem and progenitor cells (HSPCs) of patients with Friedreich's ataxia (FRDA), modified ex vivo using CRISPR/Cas9 to remove the GAA expansion mutation in frataxin
Area of Impact (as written by the applicant)	Friedreich's ataxia (FRDA), for which there is no effective treatment available
Mechanism of Action (as written by the applicant)	The proposed therapy intervention is intended to impact the target indication of Friedreich's ataxia (FRDA) via autologous transplantation of CD34+ hematopoietic stem and progenitor cells (HSPCs) ex vivo gene-corrected using CRISPR/Cas9 technology. The gene-corrected HSPC progeny will differentiate into macrophages in injured tissues and transfer functional frataxin to disease cells such as neurons in the brain, and cardiac cells in the heart. This transfer of functional frataxin to endogenous tissue cells leads to long-term tissue preservation.
Unmet Medical Need (as written by the applicant)	Friedreich's ataxia (FRDA) causes neurodegeneration leading ultimately to inability to walk as well as heart abnormalities leading to premature death. Gene-corrected HSPC transplantation may represent a one-time life-long therapy that may prevent the neurologic and cardiac complications in FRDA.
Project Objective (as written by the applicant)	Readiness for safety and manufacturing and Pre-IND
Major Proposed Activities (as written by the applicant)	• Pilot efficacy and safety studies for FDA-required studies readiness for a future clinical trial • Manufacturing development for Good Manufacturing Practice-compatible scale-up process readiness • Clinical design of the future clinical trial and pre-IND submission
Statement of Benefit to California (as written by the applicant)	Though patients with Friedreich's ataxia (FRDA) in California and the United States are rare, the technology to undergo gene-modified hematopoietic stem and progenitor cells (HSPCs) for autologous transplantation is cutting edge research and utilizes California resources including scientists and laboratories at California universities and CRO organizations in California. Once this technology is studied in the FRDA population, the technology can be used in other applications of mitochondrial disorders.
Funds Requested	$4,846,579
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 87

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	87
Standard Deviation	5
Highest	91
Lowest	70
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	1

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the 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 project have the necessary significance and potential for impact?
Yes: 13	• There are no known effective treatments for Friedreich's ataxia (FRDA). The disease onset is late, leading to progressive neurological, mobility, and cardiomyopathy impairments and death in the mid-thirties for 60-80% of individuals diagnosed with the disorder. • FRDA is a rare (approximately 1:100,000) autosomal recessive mutation caused by trinucleotide repeat amplification (GAA) in intron 1 of the frataxin gene (in more than 95% of affected individuals). There is no current treatment for FRDA. • The proposal describes an innovative approach based on the use of hematopoietic stem and progenitor cells (HSPCs) that are genetically modified ex vivo via delivery of CRISPR protein and two guide RNAs. Based on data accumulated to date and the track record of the Principal Investigator (PI) and the assembled team, in my opinion, this has a high likelihood of significantly improving patient care. • Assuming the clinical results recapitulate the preclinical studies, whereby a single infusion of modified HSPCs is sufficient to reverse symptoms, there is a potential for a highly significant impact on individuals with FRDA. • FRDA has no known curative treatment, as all therapeutics are supportive in nature. The planned approach may halt the disease, and impact not only these patients, but provide a platform for similar treatments in future. • Given there is no current treatment for FRDA, this approach could certainly impact an unmet medical need. • Yes. Importantly, the HSPC approach for ex vivo gene therapy, essentially using transfused cells as delivery systems for therapies for mitochondrial based diseases, may have broad impact. This project will broadly advance that approach, making it highly impactful. • There is a profound value proposition for patients with FRDA and similar diseases. Granted, FRDA affects a small population, but there are many similar diseases. • There are other gene therapy approaches that aim to treat FRDA that are in the clinic. The approach outlined by the applicants is unique in that it aims to correct the trinucleotide expansion in HSPCs using gene editing technology as opposed to adding a copy of the wild type frataxin gene. • I believe the approach the applicants are taking is superior to other approaches because frataxin can cause toxicities if made at supra-physiological levels. • Yes; this is an exciting proposal trying to address a difficult disease. • Yes; FRDA has a high unmet medical need.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• The applicant is building on a finding from their earlier project seeking to develop a gene therapy for cystinosis. In the cystinosis studies, the applicant made a ground-breaking discovery that HSPC-derived microglia could deliver functional cystinosin protein to diseased cells via "tunneling nanotubes" (TNT). • Using a variety of in vitro and in vivo studies, the investigator has extended that finding to show in a relevant mouse model of FRDA that the GAA edited HSPCs differentiate into tissue macrophage and microglia in affected tissues; functional frataxin is found in those tissues, and histologic and functional assays demonstrate sustained correction of the disease phenotype. In vitro studies demonstrate that the same TNT mechanism may be responsible for delivery of frataxin via transfer of mitochondria carrying the functional frataxin protein. • One concern is the in vitro assay used to demonstrate that TNT is the mechanism of transfer of the frataxin protein in the mouse model. The investigator used diseased fibroblasts as the recipient cells. This study would be more relevant if the assay were performed with cells of neuronal or muscle lineage, such as neural stem cells (NSCs) or myoblasts.

	• The applicant has excellent preclinical data showing that it's possible to deliver a gene-edited frataxin to diseased cells via transplanted HSPC. Scalability of these preclinical findings to humans is unclear but will be tested. Why intrahepatic injection though? • The applicant has achieved proof-of-concept for this approach in another disease application. • Yes. There is well-developed preliminary data on the proposed mechanism of action (MOA) – the applicant has demonstrated mitochondrial transfer from gene-edited macrophages to diseased cells via nanotubes. • What isn't clear to me is if this will scale to larger animals and humans in simple terms of cell migration to all of the impacted areas in a patient with FRDA. There isn't a clear reason why it shouldn't, but cell distribution across long distances has been a problem in other models, even with systemic integration. In other words, can enough mitochondrial transfer take place to impact cardiac function in a large animal? This may not be knowable prior to initiating the protocol but may be an issue. • Yes. There are well developed data both on the edited product and the MOA. • I believe the current data is promising enough to move forward and optimize the manufacturing process so that the product can be moved into the clinic. • While (i) animal models with human cells are always flawed and, in this case, (ii) it is not possible to conduct animal studies in the disease model with human cells because of xenotransplantation issues, I think the available data are sufficiently promising to move forward.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 13	• Generally, this is a well-designed proposal. Aspects that are well-planned include the CMC development studies. In particular, the inclusion of studies evaluating optimal loading of sgRNA and Cas9 protein as it relates to optimal gene editing efficiency will be of importance to the FDA. • They will want to know that the CMC process is optimized to minimize exposure to Cas9 and thus off-target effects. The use of protein itself is a key strategy to meet that goal. • Optimization of the gene editing protocol is crucial to balance cell survival and gene editing efficiency. To some extent this is empirical, and the applicants are aware of that. • Off-target gene editing is a crucial element for the safety of the product. The applicants are aware of this and will be measuring off-target editing. • In addition, the pilot safety studies described include a number of important elements, off-target assessment, cytogenetic assessments, in vivo engraftment with a number of important end-point assessments. • However, there are three issues that may need to be addressed to be pre-IND ready. 1) Need for dose-ranging studies in the pharmacology, biodistribution, and pharmacokinetics studies. Typically, FDA wants to see a range of doses in preclinical studies to inform clinical dosing and potential for toxicities that need to be monitored in the clinical study. 2) Currently there seem to be lack of parallels between the murine studies planned and the clinical study: isolation of sca-1+ donor cells from bone marrow rather than using mobilized PBSC as anticipated in the clinical study; and infusion of the cells via intra-hepatic injection (although details of the clinical study are not yet defined, so perhaps these will mirror well in the end). • Genomic analysis doesn't include on-target evaluation to ensure no unintended genetic changes occur at the site of gene editing. This should be done on the mid-scale production cells. • Much of the work focuses on optimization of the manufacturing process. This includes identification of clinical grade reagents and growth factors that best support the HSPC cells during gene editing. • It seems prudent to manufacture at least one batch of the mid-scale process with FRDA patient cells and analyze them for gene editing efficiency, on and off-target effects, and chromosomal rearrangements. • Another area which might lead to delays is manufacturing scale up - the applicants are aware of this and note that scale up is not always linear. However, scale up should be manageable for an autologous product. • The proposed 4-month study may not be viewed by FDA as sufficient time to assess potential for tumorigenicity. This should be discussed at the INTERACT meeting to get their guidance. • I would want to see some dose-response studies. • Why marrow derived HPSC instead of peripherally mobilized cells? • Are the time points sufficient to evaluate tumor generating potential?

	• There is a clear path to pre-IND meeting, and these studies should support the development of IND enabling studies. • The applicant has developed a well-constructed program with specific risk mitigation strategies. • Assays that will allow the applicant to clearly measure outcomes have or will be developed. This is crucial to the success of the endeavor.
No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 13	• The team comprises a highly qualified Principal Investigator who has successfully taken the identification of a gene for a rare genetic disorder to the clinic with a similar strategy. The team includes clinical experts in the disease phenotype, namely a neurologist and cardiologist, a regulatory affairs expert, the Director of a core lab with extensive experience in GMP-like manufacturing of cell and gene therapies, and a project coordinator. • The team has all of the necessary expertise to execute the study. • The two facilities have access to state-of-the-art equipment, core facilities, including a vivarium, stem cell processing, genomic medicine, and bioinformatics resources. • Use of a contractor to perform mouse studies adds another layer of expertise and capabilities to ensure all the various in-life and end-of-life studies are executed effectively. • The partnership provides access to equipment and expertise needed to develop and execute the manufacturing processes that will be needed for the clinical trial. • With additional funding provided by the institutional core, as well as the other mechanisms, the applicant has developed reasonable strategies to mitigate risks and delays. There could be delays in optimizing the manufacturing processes, but with the contingency co-funding this should be okay. • One issue is that CMC mid-scale manufacturing appears to overlap with in vivo studies that require the cells. • The milestones are well developed. • The bulk of the translation will be transferred to the partner facility, and this represents an acknowledged risk of the proposal. They will leverage standing infrastructure and agreements to execute this. • With the caveats mentioned above about empirical testing and scale up, I do think the applicants can complete the work within the timeline. • The team is well qualified, having experience with other conditions such as cystinosis. The manufacturing team is first class. • I think the main risk is the timeline rather than the ability of the team. Successful completion of the project will require some iteration on protocols and reagents, potentially impacting timeline and budget.
No: 0	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12	• This disease occurs in individuals of European, North African, Middle Eastern, and Indian origin. The investigators have access to a diverse patient population at the institution. In partnership with community services, they reach over 600,000 people in the region. • In addition, to ensure they reach the patients representing the diverse racial and ethnic backgrounds with FRDA, they will also collaborate with other medical centers including a CIRM alpha clinic, broadening their referral network. • I have confidence that the investigators will carry out the clinical trial in a manner that upholds principles of DEI. • Yes, though the section is mainly based on generic text from their institution. • Adequate DEI plan, though the DEI section of the proposal was a bit confusing, inconsistent and "cookie cutter" in its approach to DEI • Yes. However, as a genetic disorder limited to specific groups, the applicant will have limited ability to influence the diversity of enrolled trial participants. • Not directly, but this technique may be applicable to a range of diseases that impact the broader population. • Yes; there is a community outreach program in place. • FRDA is quite rare and is more frequent in white communities – however, the applicants have thought about ways to improve access to underserved communities.
No: 1	• The DEI response is generic in nature.

DIVERSITY, EQUITY, AND INCLUSION (DEI)

During the GWG discussion of the application, a GWG Board Member presented a critique and DEI score on whether the project upholds principles of diversity, equity and inclusion (DEI). DEI was discussed by the panel, and up to seven GWG Board Members provided final DEI scores and comments, shown in the table below. The responses were compiled and edited by CIRM for clarity.

DEI Score: 6

Up to 7 patient advocate and nurse 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.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	0	*none*
6-8: Responsive	2	• Adequate DEI plan, though the proposal was a bit confusing, inconsistent and "cookie cutter" in its approach to DEI
3-5: Not fully responsive	1	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-13997
Title (as written by the applicant)	Development of a Gene Therapy for the Treatment of Pitt Hopkins Syndrome (PHS) - Translating from Animal Proof of Concept to Support Pre-IND Meeting
Translational Candidate (as written by the applicant)	MZ-1866 is a recombinant AAV9 based gene therapy containing the transgene encoding Transcription Factor 4 (TCF4)
Area of Impact (as written by the applicant)	Pitt Hopkins Syndrome (PHS) is a rare genetic neurological disease which causes profound disability and severe health impact
Mechanism of Action (as written by the applicant)	Patients with Pitt Hopkins Syndrome (PHS) have heterozygous mutations in the Transcription Factor 4 (TCF4) gene resulting in haploinsufficiency. A single delivery of Mz-1866 into the central nervous system may transduce neurons to replace the deficiency of TCF4 and ultimately improve the clinical phenotype of patients.
Unmet Medical Need (as written by the applicant)	Pitt Hopkins Syndrome (PHS) symptoms include severe intellectual disability, delayed motor development, limited/no speech, constipation, autism-like behaviors, breathing problems and seizures. Mz-1866 has the potential to improve symptoms and would be the first disease-modifying treatment for PHS.
Project Objective (as written by the applicant)	The objective is to hold an FDA pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Develop a manufacturing process for a gene therapy and manufacture enough to complete rodent and non-human primate animal studies • Conduct a pilot safety, tolerability and bio-distribution study of two dose levels of MZ-1866 in non-human primates • Conduct interviews with patient caregivers to develop a deeper understanding of the disease experience and develop meaningful clinical endpoints.
Statement of Benefit to California (as written by the applicant)	It's estimated that 1 in 225,000 children are born with Pitt Hopkins Syndrome (PHS), which means there may be close to 200 families in California living with this condition. Our team will collaborate with partner organizations and vendors in our state, including Pitt Hopkins Research Foundation and Rady Children's Consortium for newborn screening and Endpoint Outcomes. Our efforts will support identification and inclusion of California families in the pursuit of a therapy.
Funds Requested	$4,000,000
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 85

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

Mean	84
Median	85
Standard Deviation	2
Highest	87
Lowest	78
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	7
(1-84): Not recommended for funding	7

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the 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 project have the necessary significance and potential for impact?
Yes: 14	• Yes. PHS is a rare genetic neurodevelopmental disorder caused by mutations in Transcription Factor 4 (TCF4) gene. There are no approved disease-modifying therapies for PHS. • Treatment of PHS is an important medical need. This is a rare genetic syndrome caused by mutations in transcription factor 4 (TCF 4). It is characterized by a loss of function haploinsufficiency, resulting in 50% of normal protein expression. • Yes. There are no curative therapies available; treatment is limited to management of symptoms. • Pitt Hopkins Syndrome (PHS) is specifically linked to the TCF, although it is not known how much gene product is needed to improve symptoms. • A single administration of a gene therapy could have a tremendous impact in patients. • This is an AAV based gene therapy that aims to over-express a functional copy of the PHS gene and restore function in patients with PHS. • Possibly - but for a small population. A future problem may be identification of patients while the defect is amenable to therapy, rather than much later when irreversible damage is done. • Ultra orphan disease - so there is limited applicability.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• Yes - the rationale is to replace a missing gene product. The gene is a transcription factor though, and understanding all affected genes is difficult. We have no idea what the required dose correction will be (i.e., what proportion of cells need gene expression restored in order for the patient to gain a normal phenotype). • The application could be strengthened by including mouse model studies wherein the treatment starts once the mice are older and/or exhibiting symptoms. These might be more predictive of what might happen in the clinic. • Yes - there is clear genetic data that link de novo TCF4 mutations to PHS. • The in vitro and in vivo data support the overall rationale. It is unclear if this is going to be effective in patients that are older and/or symptomatic. Also, the minimum effective dose and threshold are unclear. • The review panel raised questions about when to treat in the disease course and the extent of genetic correction needed.
No: 1	• The supporting data are of interest from a basic science perspective but are quite lacking in regards to a clear clinical rationale. • One of the fundamental problems in this proposal is that it is based on using gene replacement strategies early in a disease in which diagnosis occurs after symptom onset. There are no experiments to address this concern nor is there discussion of the problems that are inherent to such approaches. • A second challenge is that the goal is to replace a transcription factor. This means that there is not a secreted enzyme, as is the case for gene replacement approaches in some lysosomal storage disorders (for example). It is not clear what proportion of cells need to be fixed in order to provide improvement, and quantification is lacking.
GWG Votes	**Is the project well planned and designed?**
Yes: 11	• Yes, the planned activities will yield important preclinical data for presentation to the FDA at the pre-IND meeting. • Yes, the milestones and objectives are appropriately aligned and several activities can be performed in parallel. • Yes, but the overall manufacturing plan is unclear. The applicant includes a very generic process flow diagram for making AAV and state that they will use the selected contractor's platform manufacturing process. They have not selected a contractor, so we can't evaluate the approach.

No: 3	• From the point of view of basic research, the approach is appropriately planned and designed to test the hypothesis that replacement of TCF4 can provide clinically relevant improvements in a mouse model of PHS. • The problem is that patients are diagnosed after symptoms are present and the proposed experiments do not test the ability of a delayed treatment to repair existing defects. • There is no discussion of the problems of scaling inherent in moving this approach to the much larger human central nervous system. • It's not clear any of the planned experiments will give a clear idea of correct dose or timing. The non-human primate model will be limited. • Why not include more small animal studies looking at the effects of providing the intervention at progressive ages? • There is a real risk that this project will progress to clinical trial without the right background information, and will fail because the trial was not designed properly (even if the therapy is beneficial).
GWG Votes	**Is the project feasible?**
Yes: 13	• Yes, and several studies can be performed in parallel. Even if there are delays in the bioanalytical component or non-human primate study, those milestones are still expected to complete before Milestone 5. • One issue is that a manufacturing contractor has not been identified. This is a bit concerning since more than $2.7M is requested for the engineering batch. • The contingency plan seems reasonable. But the applicant has not taken into consideration possible delays related to the lack of availability of non-human primates (NHPs). There is a scarcity of NHPs and it is unclear how they will manage the potential lack of availability of NHPs. • Yes, viable contingency plan but see above related to NHPs. • Where the milestones and outcomes are deficient is in connecting this proposal with actual treatment in the real world. This is not only ultra rare disorder - it is also caused by de novo mutations. Therefore, there is no family history that is predictive.
No: 1	• Some concerns with feasibility.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 14	• Since the disease is ultra-rare, the applicant plans to develop a natural history database to learn more about the distribution of cases. • Genetic testing will also be performed through a company that provides genetic testing at no cost so that the underserved can also be part of the genetic testing and natural history database. • They are working with appropriate patient groups. • Adequate DEI plan.
No: 0	*none*

DIVERSITY, EQUITY, AND INCLUSION (DEI)

During the GWG discussion of the application, a GWG Board Member presented a critique and DEI score on whether the project upholds principles of diversity, equity and inclusion (DEI). DEI was discussed by the panel, and up to seven GWG Board Members provided final DEI scores and comments, shown in the table below. The responses were compiled and edited by CIRM for clarity.

DEI Score: 7.5

Up to 7 patient advocate and nurse 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.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	0	*none*
6-8: Responsive	4	• Pitt Hopkins Syndrome (PHS) is an ultra-rare disease with no current treatment. There is a substantial unmet medical need.

		• The applicant reports that, to date, no complete studies have addressed potential gender, age, ethnicity, or race differences in the expression of PHS. • Adequate DEI plan.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-13996
Title (as written by the applicant)	Overcoming resistance to standard CD19-targeted CAR T using a novel triple antigen targeted vector
Translational Candidate (as written by the applicant)	A tri-specific chimeric antigen receptor (CAR) T cell product that will prevent relapse since targets 3 different tumor antigens
Area of Impact (as written by the applicant)	Relapse associated with single or double antigen-targeted CAR T cells
Mechanism of Action (as written by the applicant)	By being able to target three different tumor antigens simultaneously on a single CAR product, there is much less of a chance the tumor evasion associated by loss of a single antigen and relapse will occur.
Unmet Medical Need (as written by the applicant)	Relapse from cancer due to antigen loss is considered a major impediment for CAR therapy. Further, by having one vector which can target all three major tumor antigens, this vector could be more widely applicable for many B cell malignancies.
Project Objective (as written by the applicant)	Data needed for pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Determine the efficiency, stability and reproducibility of the DuoCAR vector on T cell transduction • Determine the specificity and efficacy of the DuoCAR T product versus conventionally used CD19 CAR T cells • Determine any potential off-target effects or toxicities of the DuoCAR T product using a closed GMP manufacturing system
Statement of Benefit to California (as written by the applicant)	Experience with commercial CAR T products has identified that access to CAR T therapy is a key bottleneck to equitable use of this life-saving intervention. The other major issues are efficacy and cancer relapse. Our institution has a large geographic catchment, enabling it to play a crucial role in enhancing California patient participation in stem cell trials. Development of a tri-specific vector also increases patient use by targeting a broader array of B cell cancers.
Funds Requested	$4,168,679
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 83

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	83
Standard Deviation	5
Highest	95
Lowest	75
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	6*
(1-84): Not recommended for funding	7

* See Minority Report below

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the 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 project have the necessary significance and potential for impact?
Yes: 13	• There is a high unmet need to overcome relapse in CAR T treated patients with CD19 lymphoma. • Antigen loss is a known challenge faced by CAR T cell therapy and the proposed strategy addresses this with a new multi-antigen targeting CAR T cell platform. • Lower relapse rate and longer response duration would be greatly impactful. • Doctors need an additional rx for relapsed cancer patients. • There remains an unmet need for the target indication. • A high rate of relapses after standard-of-care CAR T products in B cell malignancies represents an unmet medical need. The proposed project is aimed to address the issue of relapses. • The value proposition is in the technology (triple-targeting of B-cell malignancies). It is novel and unique. The CAR technology provides an advantage over approved CAR T products because of better elimination of tumor cells, disease control and durability of response. • Immune evasion and antigen loss in CAR T is a known and significant problem. A triple antigen targeted vector is an attractive approach to addressing this issue. • This is a resubmission of a previously reviewed application. The applicants addressed some comments from reviewers. They provided a convincing explanation for skipping additional animal experiments in the model of post-CAR cell therapy relapse. However, other comments from the previous review were not addressed. • It is important to understand the clinical indication and the target patient population even at the translational stage so the appropriate plan can be developed to support an IND application. I have concerns about how this product would be studied clinically.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 10	• CAR to three antigens has efficacy over those targeting one antigen. Responded fairly well to prior critique. • The rationale is sound. It was described well in the primary application. • There are published data describing DuoCAR technology and 3-specific CAR construct, including in vitro and in vivo data • Triple antigen strategy is novel and may help to overcome issues of antigen escape
No: 3	• Yes; this is the natural next iteration of the CAR T platform. A recent strong publication supports the concept. • However, i am confused - much of the proposed work seems already completed as part of that publication. Why does so much work need to be done or repeated? Indeed, several reagents to be created in the Project Plan, such as engineered target cells, are already available and used in publications by the team. • The application states that the tri-specific construct overcomes CD22 'signaling deficits' from the bi-specific CD19/CD22 CAR product, but does not provide sufficient data to support this claim (e.g. signaling data when comparing to the bi-specific tandem construct targeting CD19 and CD22). A resubmission should include an experiment where the CD19/CD22 CAR exhibits 'signaling deficits' and show a comparison to the DuoCAR product in the same assay. • The preliminary data did not compare the in vivo efficacy of the product to the tandem CD19/CD22 CAR product that failed in the clinic (even though it was compared in vitro). A resubmission should include this comparison and a discussion of its relevance to a future clinic trial. • Preliminary data are not compelling.
GWG Votes	**Is the project well planned and designed?**
Yes: 5	• The studies proposed are appropriate and likely sufficient to support a strong pre-IND meeting. Much of the planned work appears to be already published.

	• This is a resubmission, streamlined towards a well-informed IND.
No: 8	• The applicant has already published in vitro and in vivo data using the intended vector. There is no clear justification for why the vector needs to be cloned and validated in order to have a pre-IND meeting. A resubmission should include an explanation for why Aim 1 is necessary for a pre-IND meeting. • It's unclear that the applicant needs to re-derive the vectors. • The resubmission has been streamlined but still does not make a clear case that the proposed milestones are necessary for a pre-IND meeting. The studies in Aim 2, where the DuoCAR is compared to a CD19 CAR, do not appear necessary for a pre-IND meeting. • Weakness: There is no clarity on why additional studies are necessary beyond the recently published convincing data (Science Translational Medicine 2021). It's not clear how the CAR/vector in proposed pre-IND studies would be different from the one in publication. Is the grade of reagents - i.e., GMP-grade plasmid and viral vector - the only difference? • Some proposed experiments seem not necessary. Wasn't efficacy (Aim 2) already assessed and published? • It seems they are ready for a pre-IND submission now. • It is not entirely clear what work needs to be done to be able to have a successful pre-IND meeting. • Why not compare the three antigen CAR against two antigen CAR?
GWG Votes	**Is the project feasible?**
Yes: 13	• Yes. The reagents are already available and the assays are straightforward and performed previously. • The team highlights a lot of previous experience in CAR T development. • The proposed studies are feasible. The team is well-qualified and has all resources to perform the work. • Led by expert team.
No: 0	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13	• Yes; they have responded to this critique and highlight resources at the institution that will help ensure broad recruitment from underserved communities in a future clinical trial. • This therapeutic addresses a real unmet need - relapse after CAR T therapy. This has the potential to reduce the rate of relapse and treat relapse, which is possibly a greater problem in some minority groups. • I am not sure there is a plan to incorporate perspectives in the current pre-clinical pre-IND phase of development but I don't think this is an issue at this stage. • While the preclinical studies use cells without consideration of the donors' diversity (other than male/female), the proposed clinical trial intends to enroll a broad demographic. • The applicant discussed worse outcomes among underserved communities in this disease population, so the project could support clinical development of a product that helps these underserved groups • Connection to the community is well described. • Excellent.
No: 0	*none*

DIVERSITY, EQUITY, AND INCLUSION (DEI)

During the GWG discussion of the application, a GWG Board Member presented a critique and DEI score on whether the project upholds principles of diversity, equity and inclusion (DEI). DEI was discussed by the panel, and up to seven GWG Board Members provided final DEI scores and comments, shown in the table below. The responses were compiled and edited by CIRM for clarity.

DEI Score: 8.0

Up to 7 patient advocate and nurse 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.

Score	Patient Advocate & Nurse Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
9-10: Outstanding response	1	*none*
6-8: Responsive	3	• The connection to the community is well described. • The applicant points out that blood cancers differ significantly based on gender, race, ethnic groups, i.e., inherent genetic background differences. This means that scientists are thinking about how to identify and develop therapies that overcome these differences from the get-go. • The institution's Office of Community Outreach and Engagement has achieved significant community outreach through community events (health fairs and symposiums), social media, and multi-language / multi-cultural outreach materials.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

MINORITY REPORT

If an application receives a Final Score of 1-84 and 35% or more of the scientific members of the GWG recommend an application for funding, then a minority report is provided that summarizes the perspective of those scientific members.

Scores for this revised, resubmitted application ranged from 75 to 95 but were mainly in the 80 to 86 range. The scoring panelists unanimously responded 'yes' on whether the proposal met criteria 1 (impact), 4 (feasibility), and 5 (DEI). Most (11 of 13) also responded 'yes' for criterion 2 (sound rationale). The panel was divided (5 'yes' and 8 'no') on whether the project plan and design were sound (criterion 3).

Concerns related to criteria 2 (rationale) and 3 (project plan) were shared across most of the panel - i.e., reviewers who scored both above and below 85 expressed concerns about (i) the absence of a completed in vivo study comparing triple- with duo-targeted CAR, and (ii) project plans for re-derivation of the CAR vector and replication of completed studies. Scoring and yes/no responses appeared to depend on each reviewer's level of concern weighed against their enthusiasm for the strengths of the application. Reviewers who scored the application 85 or higher described the approach as novel and unique, and stated that the proposed product had potential to improve patient care significantly. They found the preliminary data supporting the rationale to be sufficiently convincing to merit funding. Some commented that the applicant was responsive to critiques from the prior GWG review, and/or commended the expertise of the PI and project team.

Application #	TRAN1-13986
Title (as written by the applicant)	Adenine Base Editing for Autologous Hematopoietic Stem Cell Gene Therapy of CD3δ SCID
Translational Candidate (as written by the applicant)	The translational candidate is Autologous Hematopoietic Stem and Progenitor Cells from CD3δ Severe Combined Immune Deficiency (SCID) Patients Corrected by Adenine Base Editing
Area of Impact (as written by the applicant)	The candidate will provide treatment for a fatal inborn error of immunity (CD3δ SCID) affecting a genetically-isolated population.
Mechanism of Action (as written by the applicant)	Autologous Hematopoietic Stem and Progenitor cells from CD3δ SCID Patients Corrected by Adenine Base Editing have the biological activity of hematopoietic stem cells (HSC) to achieve long-term engraftment after autologous transplantation. The correction of the pathogenic CD3D mutation allows the HSC to support normal T lymphopoiesis to reverse the life-threatening SCID.
Unmet Medical Need (as written by the applicant)	By avoiding the immune complications of allogeneic hematopoietic stem cell transplantation (HSCT), autologous transplant of corrected cells should be safer: no need for a matched donor, reduced risk of treatment-related toxicity using reduced intensity conditioning, and no risk of Graft versus Host Disease (GvHD).
Project Objective (as written by the applicant)	Pre-IND meeting for guidance on IND advance
Major Proposed Activities (as written by the applicant)	• Develop Manufacturing Plan; Produce a Clinical-Scale Lot(s) of Drug Product • Perform Additional Pharmacology and Toxicology Studies • Prepare Briefing Package and Conduct Pre-IND Meeting with the FDA
Statement of Benefit to California (as written by the applicant)	Since newborn screening for SCID was initiated in California, Severe Combined Immune Deficiency (SCID) has been diagnosed in 1 of 65,000 births or about 8 patients per year. All SCID patients require hematopoietic stem cell transplantation. Autologous transplant using gene therapy may be effective and safer than transplant from a donor. Novel methods such as base editing may extend this approach to many blood cell diseases that require HSCT in California (such as Sickle Cell Disease) and could provide beneficial and cost effective therapies.
Funds Requested	$5,587,234
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 75

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

Mean	76
Median	75
Standard Deviation	8
Highest	90
Lowest	65
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	4
(1-84): Not recommended for funding	11

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the 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 project have the necessary significance and potential for impact?
Yes: 15	• Yes, CD3 delta Severe Combined Immune Deficiency (SCID) is a devastating inborn error of immunity. Patients are severely susceptible to lethal infections, often leading to infant mortality if not treated by allogeneic hematopoietic stem cell transplantation (HSCT). However, there are significant complications associated with allo-HSCT transplants and not all patients have a suitable matched donor. Therefore, there is a significant need for novel and potentially curative therapies such as the base-edited HSC product described in this proposal. • Overall, yes, but there was a lack of clarity around the studies being conducted. I found this application extremely difficult to read; with lots of abbreviations and limited clear narrative. The clarity of the application needs to be improved. • If successful, the approach is likely to be highly successful, however this appears to be a long way off. There are still preliminary results pending which may alter the outcome; for example assessing engraftment capacity of edited cells and editing levels in the long-term engrafting of HSC. • This product is of potential significance if proven successful. • Yes, if successful, this approach could become standard of care for patients. • Clear unmet medical need in a rare form of SCID (1% of the SCID-affected population). • The scope of potential impact is perhaps more limited than other projects. • The proposed base editing approach will benefit a very small patient population.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• The overall rationale is very sound and is driven by both genomic data and a deep understanding of the clinical history and manifestations of the disease. • Yes, the authors have developed a very nice set of preliminary data to support the proposed approach. They have generated a CD3 SCID cell-line disease model based on Jurkat T cells and nicely show that their base editing approach enables more consistent and superior repair of the disease-causing mutation as compared to more traditional RNP/HDR based DNA repair. • The applicants have demonstrated that their approach to base editing (adenine base editing, or ABE) is an effective technique for CD3δ SCID, but they are yet to evaluate any potential toxic effects in animal models. • The ABE approach has some merit in terms of developing a platform. An FDA INTERACT meeting should be considered essential. • The data support moving to the next stage of development. • Yes; the data support further development of the product.
No: 1	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 9	• Likely so, but the project plan is difficult to follow. Why only female mice? What toxicities will they look at, i.e. which organ toxicities and inflammatory markers? What answers does the applicant expect from the different animal studies (including longer term studies)? Why do different planned studies use different cell lines? • Overall, yes, but the project plan should be informed by the information gained from the INTERACT meeting with FDA. • Yes, the applicants have a very clear line of sight toward translating their initial pre-clinical findings toward a first-in-human IND and clinical trial. • The overall proposal is extremely well written and well-constructed and has a high probability of advancing to the next stage of development.
No: 6	• The study is ambitious and could achieve meaningful outcomes. I found the use of acronyms and/or abbreviations throughout this application very difficult.

	• Many more details are required around the use of the proposed mouse model. A detailed study plan would help. In addition,
	  • Why have the applicants chosen only to use six-week old female mice?
	  • More detail around CD34+ cells from the three different HD is needed.
	  • What happens if the applicant sees no persistence of ABE in the long term engrafting of CD34+?
	  • Why have the applicants chosen to use the proposed cell lines?
	• More details around the pilot safety studies are needed. What sort of cage side observations will be undertaken? How will organ toxicity be measured? How will any potential hematological malignancy be determined?
	• There could be significant delays associated with obtaining patient samples.
	• Lack of clarity and limited experimental details.

GWG Votes	**Is the project feasible?**
Yes: 9	• Figure 3 clearly shows that the proposed base edit leads to functional rescue in Jurkat T cells. Figure 4 clearly shows phenotypic rescue in T cells that are generated from base-edited HSCs cultured in an ATO model. However, there is no clear evidence of functional rescue of T cell function from base-edited patient-derived HSCs; it would have been good to include this preliminary data in the application. Other than that, the overall project is feasible and well-designed to meet the proposed goal of a successful pre-IND meeting. • Yes, but this is early stage since we know very little about safety - not likely ready for pre-IND in two and a half years. • With a focus on preclinical work, the project appears feasible. • Feasible, but there is long road to the clinic – with limited patient recruitment potential. • This is a top-tier team with decades of experience in the gene-modified HSC drug product development space. The team proposes to leverage their decades of platform experience to enable development of the proposed drug product. • The applicants have considered several possible risks and have devised practical and actionable contingency plans to address these potential risks. • A co-Investigator has an endowment and may withdraw up to $250,000 to be used for financial contingencies.
No: 6	• A major concern is the need for starting material for two different regulatory areas (Canada and the US) - the applicant needs to have the INTERACT meeting with the FDA before planning the project. • I recommend reapplication after the INTERACT meeting. • The mutation is rare; possibly not enough samples will be sourced for the study. • The proposed applicant team is highly qualified and appears to have all the resources in place to complete the study. • While the work proposed could be done, too many open questions remain.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12	• The development of this product will absolutely meet unmet medical needs of a very underserved racial/ethnic community, the Mennonite Community. The applicant plans to involve advocates from this population. • The applicant has engaged the relevant patient population that would be potentially benefit from this therapy. • The applicant has asked the community impacted the most to be part of the program. • The impacted community is primarily outside of CA. The applicant has included advisors from the impacted community. • CD38 SCID represents less than 1% of SCID-causing genotypes in North America overall. There is no reference to the incidence in California. Applicant may not be able to achieve the recruitment of trial participants from underserved or disproportionately affected populations in California. • Applicant has enlisted members of the Mennonite community to serve as Advisors to the program (see Letters of Support). They will participate in design of the clinical trial and patient facing materials, such as the informed consent document and other IRB-approved patient recruitment materials. • The applicant has considered the influence of race, ethnicity, sex and gender diversity. • Likely yes, though it's difficult to evaluate DEI at the TRAN stage of development.
No: 3	• Definitely impacting an underserved population, however, there appear to be fewer patients in California than in other locations.

DIVERSITY, EQUITY, AND INCLUSION (DEI)

During the GWG discussion of the application, a GWG Board Member presented a critique and DEI score on whether the project upholds principles of diversity, equity and inclusion (DEI). DEI was discussed by the panel, and up to seven GWG Board Members provided final DEI scores and comments, shown in the table below. The responses were compiled and edited by CIRM for clarity.

DEI Score: 5

Up to 7 patient advocate and nurse 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.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	0	*none*
6-8: Responsive	0	*none*
3-5: Not fully responsive	3	• Yes. This project application attempts to uphold the principals of DEI. Interestingly, CD38 SCID represents less than 1% of SCID-causing genotypes in North America. • Partially, as this applicant's work focuses on developing a strategy to correct the most prevalent pathogenic mutation identified in a Mennonite population. • Described value for the impacted community, which is primarily outside of CA. • Included advisors from the impacted community.
0-2: Not responsive	0	*none*

Application #	TRAN3-14001
Title (as written by the applicant)	Spinal subpial injection system for delivery of gene-based therapies in humans.
Translational Candidate (as written by the applicant)	Spinal subpial injection system for delivery of gene-based therapies in humans.
Area of Impact (as written by the applicant)	Spinal neurodegenerative disorders requiring targeted spinal delivery of therapeutics (Amyotrophic Lateral Sclerosis, chronic pain, spinal injury).
Mechanism of Action (as written by the applicant)	The system is an instrument designed to deliver fluid (injectable drugs, gene vectors, cell suspension) to the spinal cord and large peripheral nerves. Spinally-targeted therapies for neurodegenerative disorders (Amyotrophic Lateral Sclerosis, chronic pain, spinal injury) and which require spinally-restricted delivery of therapeutic(s).
Unmet Medical Need (as written by the applicant)	At present, no such device is clinically available.
Project Objective (as written by the applicant)	Pre-IND meeting held, FDA clinical use pending.
Major Proposed Activities (as written by the applicant)	• Regulatory - Completion of the Device Master File for the Surgical Platform • Regulatory - Completion of the Device Master File for the XYZ Manipulator • Device Development - Complete Bench Testing and Biocompatibility Testing for the Subpial Needle
Statement of Benefit to California (as written by the applicant)	Over a thousand Californians are suffer from neurodegenerative disorders (Amyotrophic Lateral Sclerosis, chronic pain, spinal injury). New treatment options are desperately needed for patients who fail standard therapies. Spinal subpial injection system (SSID) for spinal delivery of injectable therapeutics will allow Californians to be at the forefront of spinally-targeted therapies to treat neurodegenerative disorders. SSID could improve the urgent national need for a new non-opioid-based anti-nociceptive therapy .
Funds Requested	$2,665,262
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 75

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

Mean	76
Median	75
Standard Deviation	5
Highest	85
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	3
(1-84): Not recommended for funding	12

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the 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 project have the necessary significance and potential for impact?
Yes: 14	• Yes. This product allows gene therapy to bypass blood/brain barrier and would allow subpial delivery of gene products. • The development of gene therapy delivery tools to the spinal cord would clearly address a medical unmet need. • There is a need for this type of device and/or a combination product. • Yes, if the combination product regulatory path can be navigated. • This is not clear. The applicants have demonstrated that the pial membrane represents a barrier that blocks penetration of vectors to the spinal cord after intrathecal delivery. They have developed a subpial injection device, but whether this is superior to other devices that have been developed for delivery of cell based or gene based therapies to the spinal cord is not clear nor is it discussed. • This is not clear as other devices have been developed and it is not at all clear that this one has advantages over anything that already has been developed. • There is a need for a stereotactically guided spinal injection device as noted in the application. However, in terms of the value proposition, it isn't clear to me that there is freedom to operate with this device. While I am not an IP lawyer, I am aware of a very similar patented device that was used in ALS trials at another institution. It is remarkably similar to the planned device in this application. So much similarity exists that this should be addressed since this may impact the ultimate use of this planned device.
No: 1	• Minimal novel technology or evidence that it addresses an unmet medical need, since a similar device was used previously.
GWG Votes	**Is the rationale sound?**
Yes: 13	• Yes. The scientific premise of this approach is solid, and the preliminary data are supportive of this approach. It is well established that a precision injection strategy is needed to effectively deliver the cell/gene therapy to the spinal cord. • There are two affirmative answers to this issue. First, a well designed stereotactic subpial injector system will be useful with or without this indication being approved, and second, the pre-clinical data support the concept that injection with the approach achieves the stated goals of delivery of the therapeutic. This proposal does not review all of the preclinical data being developed for the IND submission, and that is appropriate. • The preliminary preclinical testing appears sound. • Based on a comprehensive set of small and large animal studies. • The rationale for the biological targets proposed is interesting, but this proposal is on the injection device itself. The rationale for a new system is not discussed, and limitations in existing approaches are not discussed. • This is not clear due to the lack of discussion regarding other devices that have been used in clinical trials for cell delivery. The need for a new system is not clear. • There is limited data supported by other publications. • No quantitative data is provided.
No: 2	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 9	• The design and interactions of this proposal are as complex as the science that they are pursuing. This is a combination product. This is requiring the work on components of the device with some mundane, but required activities as well as the pre-clinical IND enabling studies for the indications planned. • Yes. Has been reviewed by FDA with a pre-IND meeting. • A pre-IND meeting has been held. • The program is well planned, and they are dealing with a chicken/egg issue with FDA. Specifically, the FDA says there is no approved injectable cell/gene therapy, so they can't approve a device to inject a treatment that isn't approved. This is not their fault, but is an

	FDA quirk. This adds risk to the proposal of potentially funding a device for which the indication never gets to the IND stage. • To be urgent and moving things forward, the team is developing the device AND the indication that requires the device simultaneously. This is good in terms of accelerating the process, but adds risk as noted.
No: 6	• Not enough details were provided on how the project will be advanced. • The regulatory path is complex and therefore cannot be separated from the therapeutic.
GWG Votes	**Is the project feasible?**
Yes: 12	• Building and testing of the device in rats seems feasible, as does technical work on the device. • There is no doubt that anticipated technical improvements will be delivered. • Yes, multiple resources will be available to conduct the proposed activities. • While the proposed work could be done, the ultimate chance of success and eventual regulatory approval is low.
No: 3	• Not entirely clear. They need an indication for the intervention alongside the device. • Major regulatory hurdles with a combination product.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 14	• They plan to interact with a community advocacy board, though it is unclear whether this already exists. The applicant also has a community outreach program and plans to use a DEI advisory committee. • Yes. The syndrome targeted does not discriminate across ethnic/racial boundaries.
No: 1	*none*

DIVERSITY, EQUITY, AND INCLUSION (DEI)

During the GWG discussion of the application, a GWG Board Member presented a critique and DEI score on whether the project upholds principles of diversity, equity and inclusion (DEI). DEI was discussed by the panel, and up to seven GWG Board Members provided final DEI scores and comments, shown in the table below. The responses were compiled and edited by CIRM for clarity.

DEI Score: 7

Up to 7 patient advocate and nurse 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.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	0	*none*

6-8: Responsive	3	• Applicant has plans to make use of a DEI Advisory Committee, have a Community Education and Outreach Program and a Community Advocacy Board. If all 3 can be implemented this should make for a solid DEI foundation.
		• The application includes:
		  • Community Education and Outreach Program
		  • DEI Advisory Committee
		  • Community Advocacy Board
		  • CIRM Alpha Clinic

3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-13976
Title (as written by the applicant)	Autologous Hematopoietic Stem Cell Gene Therapy for Sickle Cell Disease Using a Novel High-Titer, Bifunctional Lentiviral Vector
Translational Candidate (as written by the applicant)	Autologous CD34+ Hematopoietic Stem and Progenitor Cells from Patients with Sickle Cell Disease (SCD), transduced with UV1-DS Bifunctional Lentiviral Vector.
Area of Impact (as written by the applicant)	Improve clinical outcomes for patients with Sickle Cell Disease (SCD) by autologous transplant of gene-modified hematopoietic stem cells (HSC).
Mechanism of Action (as written by the applicant)	Modification of the hematopoietic stem cells (HSC) from Sickle Cell Disease (SCD) patients with the UV1-DS lentiviral vector will lead to expression in red blood cells of two genes that inhibit sickling by different mechanisms. Blocking sickling of the red blood cells should prevent further symptoms of sickle cell disease, ideally life-long.
Unmet Medical Need (as written by the applicant)	Despite best current medical therapy, people with Sickle Cell Disease (SCD) suffer many severe medical complications and have significantly reduced survival. Gene therapy can prevent complications of SCD and improved approaches can increase efficacy and reduce costs to extend availability.
Project Objective (as written by the applicant)	The goal of this project is a pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Perform additional studies to demonstrate the activity and safety of the UV1-DS modified autologous hematopoietic stem cells (HSC) • Develop GMP-compatible methods to produce the UV1-DS-modified autologous HSC Drug Product and produce 3 clinical-scale lots. • Develop clinical trial protocol and other documents to support and hold a pre-IND meeting with FDA to obtain guidance on work needed for an IND
Statement of Benefit to California (as written by the applicant)	At least 7,000 people in California (and 100,00 across the U.S.) suffer from Sickle Cell Disease (SCD). Gene therapy provides the potential for a curative treatment by modifying the blood forming stem cells to express genes that block sickling of red blood cells and eliminate disease complications. The gene therapy being developed here will have increased efficacy and reduce costs per patient, to make gene therapy more available.
Funds Requested	$5,537,334
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 75

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

Mean	76
Median	75
Standard Deviation	5
Highest	85
Lowest	70
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	1
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the 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 project have the necessary significance and potential for impact?
Yes: 7	• People with sickle cell disease (SCD) have historically been underserved and have had poor outcomes compared to the rest of the chronic disease community. Autologous therapies that offer a one-time 'cure' would address an unmet need. • At the same time, there are clinical trials at various stages currently seeking to cure SCD. Both investigators on the application have ongoing clinical trials of an autologous gene therapy for SCD. With these in mind, I am worried about the impact of this study. • There are a number of autologous therapies in development, all of which showed promise during preclinical development. However, many of them were disappointing in clinical trials. I do think the combination of different globins and shRNA has promise. • I am worried about the insertional mutagenesis risk associated with lentiviral vectors, and patient perception of that risk – will patient perception limit adoption? • This addresses a clear unmet medical need using a combined gene / autologous cell therapy approach. • There are competing projects in late-stage clinical development – I'm not sure how well this proposal is positioned in the competitive landscape.
No: 7	• It's unlikely this product, if successful, will impact the market significantly as there are a series of products in the pipeline that are likely to be approved. • It's not clear how much this will advance the field of approaches to treatment of SCD. • Competing products have had successful clinical trials. • Combining previously successful approaches may represent an incremental improvement. • The applicant has proposed an approach to treating SCD using an optimized lentiviral vector and combining two strategies: (i) increasing fetal beta hemoglobin levels using shRNA to relieve transcription inhibition and (ii) supplying exogenous beta hemoglobin. • SCD has multiple gene therapy approaches in late stage, as well as gene editing approaches without the risks of lentiviral gene therapies (perceived or real). By the time the proposed approach reaches the clinical stage, alternate therapies will likely be approved and marketed.
GWG Votes	**Is the rationale sound?**
Yes: 9	• The rationale for the inclusion of the individual components of this vector is sound. That said, I am not convinced that such a combination is indeed necessary. • Yes, although development plans should be updated according to results from currently active SCD trials. The field is advancing rapidly, and the impact of this project may be reduced by the advancement of later stage, promising therapies in clinical trials. • The proposed project appears to have a sound scientific rationale with supporting data from both in vitro and mouse models that the vector can be produced with improved titer and improved transduction/copy number. The mouse model data indicates that the strategy reduces red blood cell sickling.
No: 5	• Does the two-pronged approach increase risk of chain imbalance? If so, it would be counterproductive. • Experimental efficacy over existing strategies appears small in Figure 9 - this is unlikely to translate to a large clinically significant effect in patients. • The field is moving away from lentiviral vectors due to the theoretical risk of malignancy. Base editing is in clinical trials now. • This approach is late to the pipeline; other strategies are ahead. • The use of lentiviral vectors is questionable in light of alternative vectors and gene editing strategies.
GWG Votes	**Is the project well planned and designed?**
Yes: 10	• Yes. Both the investigators have a lot of experience conducting such studies and this study is very well planned.

	• It's not clear which activities are critical things to getting to a pre-IND meeting. Activities are planned with several models - how will these be prioritized? • The requirement for GMP material production for the preclinical testing requires additional thought. • The path to pre-IND could be streamlined - are two mouse models needed? • From the CMC perspective the project is well planned.
No: 4	• The critical path to a pre-IND is not well defined. • Lots of emphasis on cGMP production prior to pre-IND submission. • Overall, this is a thorough program - but the rationale for the use of the two SCD animal models needs to be further explained. How will the results from the different models will be interpreted? If the study using the Berkeley model is 'successful' but the study using the Townes model is not, will the program move forward? Also, are results from both models needed to advance to a pre-IND meeting? • The critical path to pre-IND and the need for the proposed work spanning 30 months is not clear.
GWG Votes	**Is the project feasible?**
Yes: 12	• Yes, Both the investigators have a lot of experience conducting such studies and this study is very well planned. I am very comfortable that the study will be completed in the proposed timeline. • It's not clear the full time period is needed to actually get to pre-IND. • Yes, but in a very competitive space with several sickle cell therapeutics in clinical trials. • The project is feasible.
No: 2	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 14	• The application is very well developed from a DEI perspective. • The applicant shows a clear appreciation of the effect of SCD on patients from marginalized groups in California.
No: 0	*none*

DIVERSITY, EQUITY, AND INCLUSION (DEI)

During the GWG discussion of the application, a GWG Board Member presented a critique and DEI score on whether the project upholds principles of diversity, equity and inclusion (DEI). DEI was discussed by the panel, and up to seven GWG Board Members provided final DEI scores and comments, shown in the table below. The responses were compiled and edited by CIRM for clarity.

DEI Score: 9

Up to 7 patient advocate and nurse 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.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	2	• Yes. According to the applicant, in California, there were approximately 6,200 people with SCD and 43% were younger than 18, 21% were between the ages of 18 and 29, 25% between the ages of 30 and 50, and 11% were 51 and older. • The Project Plan reflects gender and ethnic sensitivity. The applicant will try to obtain healthy donor and SCD CD34+ cells from individuals from underserved demographic groups including Black and Hispanic populations. Sex will also be incorporated into the SCD mouse model studies by using SCD cells from both male and female mice.
6-8: Responsive	1	• Strong DEI component.
3-5: Not fully responsive	0	*none*

0-2: Not responsive	0	*none*

Application #	TRAN1-14018
Title (as written by the applicant)	The First Orally Delivered Cell Therapy for the Treatment of Inflammatory Bowel Disease
Translational Candidate (as written by the applicant)	We are developing the first orally delivered allogeneic mesenchymal stem cell therapy (MSC) for the treatment of inflammatory bowel disease (IBD)
Area of Impact (as written by the applicant)	IBD is large unmet medical need >2 million patients in US, >70% fail current standard of care, an oral cell therapy delivers cells directly to inflamed site
Mechanism of Action (as written by the applicant)	The anti-inflammatory cell payload is deployed to the inflamed intestine and colon. The initial effect of the deployed cells is to attenuate neutrophil infiltration and calprotectin secretion to begin anti-inflammatory effects. The administered cells also affect the local immune tissues e.g.-mesenteric lymph node and spleen by release of anti-inflammatory mediators to further quell inflammation (↓IL6, ↓ TNF a , ↑ IL10) and restore homeostasis.
Unmet Medical Need (as written by the applicant)	2 million people in the US are afflicted with IBD. For unknown reasons, the incidence is increasing and there is no known cure. Current standard of care is effective in only 1/3 of patients. The other 2/3 experience refractory disease, greatly diminished quality of life and eventual surgical intervention.
Project Objective (as written by the applicant)	To gather all remaining data to file an FDA pre-IND
Major Proposed Activities (as written by the applicant)	• CMC: Oral Formulated Cell Therapy cGMP-compliant Manufacturing Studies to gather all materials necessary to populate Manufacturing section of pre-IND app • CMC: Final pre-IND-enabling Non-Clinical Studies necessary to populate Non-Clinical portion of pre-IND app • Collaborate with all team members to effectively submit an FDA pre-IND
Statement of Benefit to California (as written by the applicant)	The current standard of care works in only a third of IBD patients. IBD incidence is growing in California and elsewhere, and there is no known cure. Cell-based therapy is considered the next generation treatment but is only available to those who have access and/or live near a specialized cell therapy clinic or hospital. By pioneering a new oral route of administration, we will grant most sufferers of IBD access to this and other breakthrough cell-derived therapies.
Funds Requested	$1,822,685
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 70

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

Mean	71
Median	70
Standard Deviation	6
Highest	84
Lowest	62
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	0
(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/RFA. Following the panel's discussion and scoring of the application, the 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 project have the necessary significance and potential for impact?
Yes: 12	• Yes. Despite available treatment options, there continues to be significant morbidity associated with Crohn's disease including abdominal pain, nausea, diarrhea, weight loss, rectal bleeding, and decreased quality of life, as well as potential for serious and life-threatening complications (cancer, gallstones, bowel perforation, ulcers, fistulas, other) and need for surgical intervention in some cases. • Yes, there is potential impact for an alternative therapy for IBD. Since the current standard of care often fails, this could provide an alternative treatment for all IBD patients. • If successful, the product has the potential to be highly effective in all patients with inflammatory bowel diseases. • Yes, the option of alternative therapy as compared to current standard of care would be impactful for both patients and healthcare providers. • The project is unique in that it aims to deliver oral anti-inflammatory mesenchymal stem cells to treat inflammatory bowel disease. • The product has been through extensive in vitro and in vivo experiments; these have shown the product can be manufactured, stored and delivered effectively. Preliminary results have demonstrated the product reaches the target cells within hours and acts to decrease inflammatory cell infiltrate. This now warrants further investigation for delivery via the oral route rather than endoscopically. • If successful, the proposed product has potential to significantly improve patient care. Knowledge learned during development regarding this novel route-of-administration and required technology to enable oral formulation of cell-based therapies likely has potential implications for development of new therapies for other indications. • Yes, the applicant would be provided the opportunity to move their product forward by manufacturing newly formulated drug product and to perform additional nonclinical studies. • If successful, yes, the proposed product offers a positive value proposition to patients, based primarily on the continued high unmet need in this patient population and assumed ease of administration which may translate to greater and easier access to effective treatments. • IBD important. Oral meds would be advantageous. • Oral delivery of cell therapies could have a tremendous impact on the field, though it's not clear from this application that it can be effective.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 8	• The rationale is supported by preceding nonclinical and clinical data related to the proposed project. • The project builds upon previous scientific findings, including demonstration of the product's safety, bio-distribution and tumorigenicity. • Mouse models have shown optimal doses and increased anti-inflammatory factors. The product has also been tested in intestinal organoids. • In the sense that the development of technology that enables oral administration of cell-based products (that in turn have clinical effect), the rationale is compelling. This would be meaningful and likely have great impact, however the technological hurdles are likely numerous and significant. • The applicant has conducted numerous pilot, early research, and exploratory proof-of-concept studies in animals and in vitro-based pharmacology models, which have generated some interesting data to support the approach. Data overall appear preliminary though, and some conclusions of studies do not appear to be adequately supported. • Data are interesting and merit further investigation, but should be considered preliminary. Data from some studies may have been over-interpreted. • Overall, the premise of this project is sound, but notably remains to be proven for administration as oral capsules. To date, there is little to no data on the product as it is proposed to be manufactured and formulated. However, preliminary data may indicate the

	utility of additional research and development activities. Some of the data presented in figures was difficult to interpret as the details surrounding how the experiments were performed and how the samples were analyzed was lacking. ● Strongly recommend continued research to better understand many aspects of the proposed product and route of administration, including better characterization of the product's mechanism of action, optimized formulations, confirmation of sufficient cell survival following encapsulation and oral delivery, and critical quality attributes of donor cell lines. ● In many of the studies, it is unclear if they evaluated the intended clinical product. Applicants should include the selected donor cell, formulation, encapsulation, and other areas for each study. ● It would be helpful to better understand potential donor to donor variability and thus better understand critical quality attributes for selection of donor cell lines. It is unclear if multiple donor lines have been tested. ● The applicant does not anticipate cell survival beyond short periods of time following oral administration, potentially as short as 24 hours, and the specific site of desired cell delivery following oral administration is not stated or clear from animal data presented. It would be helpful to better understand how this short survival as well as the applicant's hypothesized mechanism of action would translate to the clinical scenario. For example, does the product need to be administered daily? For how many days? During flare-ups only? Similarly, a better understanding of dose level extrapolation between animals and humans, again based on the hypothesized mechanism of action, is needed. For example, would dose levels be calculated based on required number of (viable) cells per unit area of the intestines, or colon, or other? The applicant states that they are extrapolating dose levels based on allometric scaling / body surface area calculations, which does not appear appropriate based on the products hypothesized mechanism of action. Both of these points and others could have impact on planned manufacturing. ● The applicant's cell distribution data were a little confusing and hard to interpret. Are data showing also cell distribution to lung tissue within 4 hours? ● The product has also been shown not to lead to growth of tumors, although I am not sure as to why the applicants have put such emphasis on this. A clearer explanation for this would have been helpful. ● While agree that tumorigenicity is likely a low concern given that this is an MSC-based product and route of administration is likely to prevent cell survival beyond very short periods of time (and furthermore that FDA is unlikely to require a tumorigenicity study), there are some concerns with the design of this study and the applicant's conclusion that the data establish that there is no risk of tumor formation. For example, the low number of animals used, the short study duration, unclear which tissues were collected, and most notably the presumed lack of cell survival following administration. It would be more helpful if the applicant first comprehensively understood and characterized the kinetics of cell distribution and survival. This may be more of an issue of resources (time, money, use of animals) not being efficiently allocated. ● The applicant concluded that the proposed product is safe, based on results from a study conducted in mini animal models. This does not appear to be an adequately designed safety/toxicology study and unlikely to satisfy regulatory requirements. The conduct of this study appears premature.
No: 5	● Some good preliminary data. ● It appears that the proposed MOA requires intact cells to be delivered to the gastrointestinal tract and other immune organs. However, there was only PCR-based data showing DNA was detected in those tissues (and only in the first 24 hours). A resubmission should attempt to track the cells in animals after administration to demonstrate this concept and support the proposed MOA. ● Lack of details with preliminary data, and significant concern with generating cGMP cell production and IND-enabling studies prior to a pre-IND with the FDA. ● Proposed potency assay needs improvement. ● Numerous technical, chemistry manufacturing and controls (CMC), and regulatory issues.
GWG Votes	**Is the project well planned and designed?**
Yes: 2	● Five clear milestones were identified. Milestone one, program planning and management should already be in place. I would have expected the project should have a well-conceived study plan and team to execute the plan in a timely manner. Whilst I appreciate not all team members may be recruited, having a plan and developing good communication techniques should not be a milestone and should not take four months.

	• Milestone 3 is clearly articulated but carries the biggest risk in slippage with all the animal models being conducted. They are important studies but challenging.

No:
11
	• There appear to be opportunities for acceleration, particularly if the applicant pursues the pre-IND first and receives advice that may streamline development.
	• I am concerned that the timeline would slip significantly without a better plan at the beginning, instead of using the first 4-6 months to put a plan together.
	• Milestone 1 should be in place already.
	• No, the project is not well-planned. The applicant proposes numerous activities culminating in preparation and submission of an FDA pre-IND package in months 15-18. This is an issue because the applicant is also proposing other activities in advance and before the pre-IND meeting including cGMP manufacturing studies of the product and nonclinical safety and efficacy studies. It is critical that the FDA have opportunity to provide detailed input on these plans prior to initiation, given the required time and expense of these studies and some concerns over the proposed approaches.
	• It appears feasible that the applicant could pursue a pre-IND first and immediately. At a minimum, the applicant should not conduct any additional safety studies without FDA input on the study designs, but would further recommend that the applicant withhold from initiation of any additional animal studies until after FDA can comment. Feedback on proposed IND-enabling safety/toxicity studies and/or animal studies that will determine dose level selection in the planned clinical trial are appropriate topics for an FDA pre-IND meetings.
	• It is unclear if the planned safety and efficacy studies are sufficient to meet regulatory requirements, and thus could result in the need to conduct additional studies after the applicant receives pre-IND feedback. This is a significant risk that is avoidable. Furthermore, learnings from the completion of milestone 2 (cGMP manufacturing) may result in the need to change the product which then itself could promote the need to conduct additional IND-enabling animal studies.
	• Potentially, if the sequence of activities is adjusted. The team should consider conducting milestone 2 (optimizing product manufacturing) and pre-IND meeting prior to conducting additional animal studies.
	• The current proposal is not well-planned from a CMC perspective. There are a number of issues with the plan as currently written. The CMC proposal needs additional work.
	• With regards to the manufacturing plan, very few details were given regarding the alginate encapsulation or the packing into enteric capsules. There were also no characterization data nor proposed release specifications around the encapsulated beads alone or in the capsule as final drug product. Additionally, very little information was given regarding the MSC donor process and characterization.
	• Insufficient info on manufacturing process.
	• For manufacturing, it is unclear as to the cell count expected to be attained from a single manufacturing run, and thus a single batch; and then, how many capsules could be produced from a single batch. The proposed plans include a large number of studies, which will require a large number of capsules. In addition, the filling process is completely manual as far as outlined in the proposal. Is it achievable to manually fill hundreds of capsules under cGMP at the manufacturing site?
	• It is unclear which cytokines will continue to be analyzed. For example, the test listed under identity states "gene expression" however the specific genes or gene products are not delineated.
	• There are a number of issues with the lot release tests listed:
	  ◦ Purity tests are actually safety tests.
	  ◦ Flow cytometry is used for both identity and purity.
	  ◦ Gene expression is not an identity test. Which genes will you evaluate?
	  ◦ A number of tests are missing: cells/capsule testing (eg. homogeneity of your batch, capsule strength), residual testing (eg. residual trypsin, other manufacturing raw materials).
	  ◦ Karyotyping is typically performed on the cell bank, not each lot of drug product.
	• In vivo and tumorigenicity are not lot release tests for potency.
	• The proposed potency assessment is flawed. There are two assays that you will need, a pseudo-potency assay for pre-IND and a cell-based bioassay for bioactivity.
	  ◦ The pseudo-potency assay should be quantitative assessment of one or more important cytokines.
	  ◦ The bioassay should be cell-based in which you show the mechanism of action of your drug product. If you are attempting to decrease an inflammatory response, you need an inflammation bioassay. This assay should, minimally, be in development at pre-IND.

	• The stability proposal is flawed. Note, the proposed ambient temperature should be controlled and monitored, typically 18-25C, for the stability study and the shipping study. Also, the timepoints should be closer to International Council for Harmonization requirements (e.g., 0, 1, 3, 6, 9, 12, 18, 24 months). Finally, the typical testing panel includes all tests except safety (while sterility is needed at the final time point). • Capsule load would be too high for patients.
GWG Votes	**Is the project feasible?**
Yes: 6	• Partnership with a contract research organization is excellent. • Yes, feasible but recommend significant changes. The team appears capable of performing objectives. This should be revisited after the team meets with the FDA, as this meeting is likely to significantly influence development plans. • The team appears to be engaging appropriately with consultants to support execution of plans, but some concerns remain regarding the specific strategy of initiating some of these activities prior to a pre-IND meeting with the FDA. This is potentially a major issue. • There are CMC issues and lot release issues. • I was surprised to see a senior research scientist is still to be hired for this project.
No: 7	• What is proposed would likely not result in a successful pre-IND/IND submission. • Additional staff are needed to support the outsourced manufacturing and testing. • The applicant does not anticipate CMC challenges, and therefore has not planned appropriately. • Manufacturing plan seems underdeveloped. • Only have access to necessary resources in the preliminary stages for CMC. • Not enough information on the characterization of the spheres - only on the cells. This would be important to address before the next phase. • Ambitious timelines.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 11	• Yes. This project will enhance the care of IBD for all patients, regardless of gender, race, age or financial ability. • Appropriate. • Some upholding of principles/aims to provide a treatment that could reach the target community. • Seems adequate.
No: 2	*none*

DIVERSITY, EQUITY, AND INCLUSION (DEI)

During the GWG discussion of the application, a GWG Board Member presented a critique and DEI score on whether the project upholds principles of diversity, equity and inclusion (DEI). DEI was discussed by the panel, and up to seven GWG Board Members provided final DEI scores and comments, shown in the table below. The responses were compiled and edited by CIRM for clarity.

DEI Score: 8.0

Up to 7 patient advocate and nurse 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.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	0	*none*
6-8: Responsive	4	• IBD is prevalent across all gender, ethnic, race, and other groups, although it is more prevalent in some groups. The incidence is increasing across all groups. • While the need for effective treatments for IBD impacts all groups, even drugs that are only partially effective cannot survive the

		transport / storage for provision to remote and temperature-extreme communities. • They make an attempt given the challenge of doing so with a TRAN proposal.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-14022
Title (as written by the applicant)	Cone progenitor cells for prevention and treatment of retinal degeneration
Translational Candidate (as written by the applicant)	Human cone progenitor cells
Area of Impact (as written by the applicant)	Retinal degenerative disease resulting in loss of central vision
Mechanism of Action (as written by the applicant)	In pre-clinical studies, cone progenitor cells (CPC) are neuroprotective, they improve survival of the eye's cones and rods, likely through paracrine effects. Further CPC integrate efficiently into the retina after subretinal injection, generating new cones in their correct anatomic position. This cell replacement effect is also likely a mechanism of action in improving visual function.
Unmet Medical Need (as written by the applicant)	There are no approved therapies for inherited retinal diseases causing central vision loss, or for 'dry' age-related macular degeneration with central vision loss. So, central vision loss, whether inherited or acquired, represents a large unmet medical need.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• (Feasibility run) GMP-CPC meeting release criteria sufficient to proceed to engineering run CPC • Engineering run GMP-CPC sufficient for use in NHP dose-finding studies and justifying proceeding to clinical batch manufacture • Pre-IND meeting scheduled (pre-IND documentation submitted)
Statement of Benefit to California (as written by the applicant)	Loss of central vision from inherited retinal diseases (IRD) is quite rare, but affects young people, and has no useful therapy. Central vision loss from age-related macular degeneration (AMD) is quite common in more elderly people in CA (and across US), significantly impairing quality of life (QoL), and costing the US health system at least $9B/year. No approved therapy is available for dry AMD. CPC have the potential to slow and even reverse vision loss, improving QoL, in both IRD and AMD.
Funds Requested	$4,037,829
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 70

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

Mean	71
Median	70
Standard Deviation	4
Highest	75
Lowest	65
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/RFA. Following the panel's discussion and scoring of the application, the 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 project have the necessary significance and potential for impact?
Yes: 9	• If the product can be successfully produced, this product could impact unmet medical need in certain inherited retinal diseases. • There is still an unmet need for inherited retinal diseases (IRD), especially cone progenitor cells (CPC). • The applicants outline a novel approach to treating IRDs with CPCs. If successful the approach might be used in a number of retinal conditions that currently have limited options for treatment. • If the methodology proves successful, the approach outlined for isolating and propagating only specific cell type (e.g. cone) may be useful for pursuing treatments in other diseases. • If the treatment proves efficacious and safe, the treatment would be highly impactful for a population without highly effective treatment. It is unclear what the duration of treatment would be. • It is not yet clear if a single administration of the product would be sufficient, but if so it would offer a significant impact for patients.
No: 5	• Unclear manufacturing strategy.
GWG Votes	**Is the rationale sound?**
Yes: 9	• The general framework for the project proposal to replace cone cells is sound. • Rationale is sound. • The rationale that CPCs could be used to treat IRDs is sound and supported by limited animal data. • To the limited extent of preclinical data available, the data is supportive. Typically there is more preclinical work done in similar projects. A better understanding of a number of aspects such as duration, engraftment, and effect with other cells is needed.
No: 5	• The initial rodent data suggests that the product might work (though ERG data was inconclusive in rats), but the small numbers and pooled experiments make it difficult to interpret whether the treatment is showing good efficacy. • Preliminary data are under-developed. • The preclinical data are not convincing. • Weak preliminary data; very little evidence this works. • The provided data are difficult to follow. For example, the application states that engraftment is 'highly efficient' but only refers to staining of one sample where the cone cells appear in the expected anatomic location. ERG measurements in rats were inconclusive, and the figure for mouse results suggests statistical analysis was performed but does not indicate what the p values are. Figure 5 is the 'results of two experiments' that were pooled, saying the first experiment was stopped, but it is not clear if it was stopped prior to the 60 day time point or how many animals were evaluated at each time point.
GWG Votes	**Is the project well planned and designed?**
Yes: 2	*none*
No: 12	• The application was not very detailed and, in some cases, quite difficult to follow. Additionally, given the number of entities involved and the as of yet unassigned specific personnel, it is difficult to ascertain that all necessary planning is in place. • The plan is hard to follow with insufficient data on manufacturing and product stability. • The plan focuses on GMP manufacturing, which seems premature at this stage. GMP-grade product is not necessary for providing stronger data to support efficacy. • The project puts the bulk of its emphasis on GMP manufacturing. Yet the manufacturing section was missing key information for assessment. It would be beneficial to have more emphasis on demonstrating promise in pre-clinical models. • This application is extremely hard to read and comprehend. From a manufacturing perspective, I find myself asking many of the same questions I asked last time. Apart from

	a cartoon and now being told that the initial expansion of cells is on extracellular matrix coated plates there is no detail outlining how this product is manufactured. ● There is no information on genetic stability of cells given they undergo extensive proliferation. Have the cells been karyotyped at various stages in the manufacturing process? ● Is all culture adherent or is some of it in suspension? ● What media and growth factors are used? ● How expandable are the cells? Not how far have you expanded them but how expandable are they? This is important as the greater expansion that can be obtained while maintaining functional and genetic stability the better off they are from a batch manufacturing perspective. ● The plan prioritizes speed to the clinic, but does not appear to emphasize collecting solid efficacy data in animal models of disease in order to understand the pharmacology and dosing of the product. ● The planned large animal study will be performed in healthy animals so no real efficacy readout is possible. It is not clear how the large animal study is "dose finding", though it could provide information related to the delivery procedure and device. ● Several parts of the application are confusing. For example the application also mentions "GLP-efficacy studies" which does not make sense because GLP compliance is only required for pivotal safety studies. The team might benefit from more support from a product development expert. ● In the prior submission we also had the benefit of FDA feedback from their INTERACT meeting. This time we have an incomplete summary of FDA interaction from notes taken by the applicant. ● The translational strategy not clear. The IP strategy difficult to understand. ● The company has minimal staffing and unclear capacity to execute the project. ● Very hard to follow application.
GWG Votes	**Is the project feasible?**
Yes: 9	● A great deal of work will depend on the alliance with a contract development and manufacturing organization (CDMO) and the contract research organization (CRO). ● Given that all the team members are not yet assigned, this cannot be fully determined. The core team is extremely limited. To drive a clinical program, the critical roles usually are preferred to be in the main company. ● There appears to be only one employee at the applicant institution, and the remaining key personnel are mostly at contracting organizations. It is not clear who is handling the animal work and reviewing the data. The project manager and others are listed as "TBD." The CMC consultant is listed as 1% effort. This team profile gives concern that the right experts are not in place to make this program a success. ● The applicant institution has very limited resources and will rely heavily on their partners. ● This will depend on the smooth and timely tech transfer of the applicants process to the CDMO. Tech transfer is always more difficult than one imagines and while it appears from their website that the CDMO has the infrastructure in place to handle this project I am still concerned that the tech transfer process will lead to delays in the timeline. ● The project is feasible but the use of GMP grade product for pilot studies is not appropriate. ● There are some contingencies built into the manufacturing plan but other issues I raised in the last review like genetic stability have not been addressed. ● It is unclear from the information provided whether the applicant has the necessary resources and a viable contingency plan in place.
No: 5	● More pre-clinical work needs to be done before moving into pre-IND and cGMP production. ● The feasibility is unclear given the lack of information in relation to the manufacturing process. ● Unclear manufacturing strategy.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 2	*none*
No: 12	● While the treatment would be applicable to a range of populations, it was unclear whether the treatment would reach all. ● It is not clear how prevalent this indication is in underserved communities, or whether the applicant fully understood what was to be provided in this section of the application.

	• The project is largely about manufacturing and testing a cell therapy product before moving towards clinical trials, but even so it does not appear that a lot of thought has gone into DEI considerations. • The focus of the documents were largely around the science/manufacturing. Limited information on this aspect. • It is unclear from the information provided whether the applicant will incorporate perspectives in the implementation of the research project. • Inadequate effort to address DEI. • Information provided is not adequate.

DIVERSITY, EQUITY, AND INCLUSION (DEI)

During the GWG discussion of the application, a GWG Board Member presented a critique and DEI score on whether the project upholds principles of diversity, equity and inclusion (DEI). DEI was discussed by the panel, and up to seven GWG Board Members provided final DEI scores and comments, shown in the table below. The responses were compiled and edited by CIRM for clarity.

DEI Score: 3

Up to 7 patient advocate and nurse 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.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	0	*none*
6-8: Responsive	0	*none*
3-5: Not fully responsive	2	• Planned activities are incomplete or inadequate and may not reflect a good faith effort for outreach and engagement of patients from underserved groups. • The applicant states they will focus on recruitment of California-based trial participants that reflect the state's rich diversity. However, there is no well-conceived plan to achieve these enrollment goals.
0-2: Not responsive	1	• DEI is not addressed sufficiently.

Application #	TRAN3-14004
Title (as written by the applicant)	Clinical translation of MPI for cellular imaging of CAR T cells
Translational Candidate (as written by the applicant)	MPI Cellular Imaging for Monitoring Cell Therapy Treatment of Brain Cancer. MPI is a 4D imaging device for labeled cells.
Area of Impact (as written by the applicant)	Clinical MPI will enable tracking of location, migration, persistence, and quantity of cells during cell therapy
Mechanism of Action (as written by the applicant)	The Magnetic Particle Imaging (MPI) System, comprising an MPI Imager + MPI Tracer, is intended for use by appropriately trained health care professionals for physiological assessments such as but not limited to the location, migration, persistence, and quantity of cells following administration into a human body. When interpreted by a trained physician, the images produced by the system yield information that may be used to drive clinical management.
Unmet Medical Need (as written by the applicant)	MPI addresses the urgent unmet medical need caused by the inability of existing technologies to perform longitudinal imaging studies of cell therapy. This information is critical for research, diagnosis, therapeutic planning and therapeutic outcome assessment.
Project Objective (as written by the applicant)	Submission of an IDE to test MPI on patients
Major Proposed Activities (as written by the applicant)	• Verify that cell tagging protocols cause a negligible change in cell function. Verify that the clinical scanner has sufficient detection sensitivity • Validate our target indication sensitivity and efficacy in preclinical model of CAR-T cell therapy treatment of breast cancer with brain metastases. • Verify MPI magnetic safety on volunteers and prepare FDA submissions to enable clinical feasibility trial.
Statement of Benefit to California (as written by the applicant)	Equitable and timely access to affordable cancer therapy is key to addressing healthcare discrepancies in California. The proposed work will develop a new cellular imaging technique that will lead to faster, more successful development cycles for cancer immunotherapies. This will directly benefit the citizens of California by improving survival rates from solid tumors and delivering cost reduction for cellular therapies associated with better survival rates and faster development times.
Funds Requested	$1,984,740
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

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	3
Highest	70
Lowest	60
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/RFA. Following the panel's discussion and scoring of the application, the 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 project have the necessary significance and potential for impact?
Yes: 4	• The proposal to upgrade the existing MPI machine to clinical grade would be an achievement for possible clinical application in the future. • The proposed improvement of spatial resolution will be an impactful development for MPI technology. • The machine can be used to track magnetic particle-based therapy such as hyperthermia. However, the proposed tracking of CAR-T cell migration and accumulation may not be as useful as the PI is hoping for. • Tracking stem cells (or CAR-T) to the site of interest may not be impactful as the MPI machines still lack tomography images and resolution considering PET/SPECT/MRI. Moreover, long half-life positron isotopes can be used to label CAR-T cells and the precise location of the cells in the solid tumors can be delineated with confidence due to the capability of high-resolution tomographic images co-registered with corresponding CT or MRI. The cells can be tracked over 7 days with ease.
No: 10	• The significance of the problem is clear - we don't know how CAR-T cells behave in patients and better knowledge of this would inform clinical development of these therapies. • If it works to provide the data hoped for (longitudinal imaging), it could be a significant aid in the evaluation and development of CAR-T and other adoptive cell therapies. I am not sure if this would be incorporated in clinical decision making anytime soon. • It appears that the imaging could be used to provide early images that demonstrate that a cell therapy is not likely to work, but at that point the cell therapy and imaging costs would have already been incurred, so the value is not obvious. • The advance over already available and clinically used techniques is not clear. • It is not yet clear what the exact need is. There is limited information provided that demonstrates an unmet need to know the location of cell therapies after administration. While it is true that there may not be much data from human patients regarding the location of adoptive cell transfer after administration, there was not a strong case made for why that information is a gap in cancer care. • Not clear what the impact of this technology would be. Why do you need to know here the CAR-T cells go? This is too early in development to complete with nuclear medicine. • Unclear if this will provide all of the information they intend to, given limitations that are not well addressed.
GWG Votes	**Is the rationale sound?**
Yes: 4	*none*
No: 10	• The product will help accelerate the development of MPI technology and application, however, it may not be as impactful for stem cell technology. • Tracking stem cells using MRI or nuclear medicine technology are already developed and been used. The recent development of label-free stem cell tracking will eventually replace all labeling-based cell tracking. • The current resolution of MPI will not be able to determine the exact position of the cells in the brain, whether it is remaining in the tumors or in the surrounding tissues. The main issue will also be with intraventricular injection. • Resolution appears rather poor. • The proposal states "Magnetic Particle Imaging (MPI) is an emerging clinical imaging modality that will allow clinicians to monitor a cancer patient's cell therapy location, migration, persistence, and quantity." However, this does not take into account the dynamics of cells in vivo. ◦ What about dead/dysfunctional T cells which will still lead to signals or other mechanisms of movement of the label such as exosome transfer, or uptake by macrophages for instance?

	● What about proliferation and dilution of signal/cells? Combined with some labeled T cells trafficking or dying, this could cause false negative results. Thus, the power to correlate imaging signal with actual T cell function is unclear. ● There is preclinical data on use of MPI to detect labeled cells in vivo. However, there is not an evaluation of how the dynamics of T cell behavior proliferation, dysfunction, migration can be interpreted properly with MPI. ● Not clear whether CAR-T cells can really be dynamically imaged - dead and phagocytosing cells may cause confounding data. ● The connection between cell distribution and clinical outcome is not clear. ● Technology should be used for something else. ● Rationale is not convincing for presented application. ● Cell labelling of this type is not approved in USA.
GWG Votes	**Is the project well planned and designed?**
Yes: 3	● The project will help to validate MPI. ● The planned activities are appropriate for the milestones, though the prototype machine is for scanning the head only.
No: 11	● The plan for evaluation of T cells is limited. Given the concerns about truly tracking active CAR-T cells, more robust immune measurement including of the CAR-T cells in vivo in addition to the proposed histology is critical for interpreting the MPI data and correlating with actual in vivo activity. ● T-cell dynamics need to be investigated. ● The use of the proposed cells for labeling may not be useful for labeling T-cells. PI should use CD3+ cells from PBMC or bone marrow throughout the studies. ● Available data is from an older version of MPI technology where the resolution is poor. ● The discussion on potential risks is quite limited. Risk 1 begins to address the issue of limited power to measure persistence but the management strategy is not articulated at all. ● If sensitivity or resolution is an issue, they plan to "use a new nanoparticle better suited to MPI than ..." which they intend to use in the final clinical product. Why not test that at this stage? ● Unclear how are volunteers being tested for safety thresholds? Head? Or arm and leg? ● The time frame to licensing seems a long way away.
GWG Votes	**Is the project feasible?**
Yes: 10	● Yes, the proposed work is doable given the experience of the team. ● Some team members are still to be hired, but the rest of the team is qualified and well-organized into a project structure that should be efficient. ● Key outside personnel (e.g. consultants) have been identified.
No: 4	● The timeline proposed to meet with the FDA and get the technology for clinical use may not be feasible.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 7	● The initial application of the technology is aimed at a cell therapy, in which there is an unmet need and economic disparities for cancer survivorship. ● Excellent.
No: 7	● If this works, it would serve an unmet need across the diverse population. ● They will work with clinicians and patient groups to incorporate diverse perspectives during phases of product development. ● It is unclear how “Clinical MPI is expected to lead to a cost reduction for cellular cancer therapies, due to improved survival rates and faster development cycles” would make cell therapies more accessible. ● Inadequate development of these in the project. ● Needs to discuss the impact on the diverse patient populations.

DIVERSITY, EQUITY, AND INCLUSION (DEI)

During the GWG discussion of the application, a GWG Board Member presented a critique and DEI score on whether the project upholds principles of diversity, equity and inclusion (DEI). DEI was discussed by the panel, and up to

seven GWG Board Members provided final DEI scores and comments, shown in the table below. The responses were compiled and edited by CIRM for clarity.

DEI Score: 4

Up to 7 patient advocate and nurse 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.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	1	*none*
6-8: Responsive	0	*none*
3-5: Not fully responsive	1	*none*
0-2: Not responsive	1	• No meaningful discussion of the impact on traditionally underserved communities, no description of unmet need, no discussion of patient diversity, no discussion of the challenges in developing a product for underserved communities. • Reflects a plan to include diverse perspectives.

Application #	TRAN4-14015
Title (as written by the applicant)	Improving HSC and PBMC Fraction Quality by Enhancing Cord Blood and Leukopak Storage Using Novel Cryoprotectants
Translational Candidate (as written by the applicant)	DMSO-, protein-, serum-free and chemically defined cryopreservation solutions that utilize novel cryoprotectants.
Area of Impact (as written by the applicant)	Cryopreservation in general, batch processing of cell therapies, patient safety by removing DMSO, improving quality of raw materials.
Mechanism of Action (as written by the applicant)	The mechanism of action [was left blank by the applicant].
Unmet Medical Need (as written by the applicant)	The quality of raw materials such as cord blood and apheresis is critical to the manufacture of many cellular therapies. The field of bioprocessing is strongly reviewing all aspects involved with acquiring high quality raw materials and the storage and transport is of primary concern to improve.
Project Objective (as written by the applicant)	Improve preservation of raw materials, ie. apheresis.
Major Proposed Activities (as written by the applicant)	• Preparation of cryopreservation formulations, improvements to formulations. • Cryopreservation study of cord blood and apheresis to examine advanced cryopreservation solution effects on raw material preservation. • Non-frozen preservation study of cord blood and apheresis to greatly extend shelf life without ice.
Statement of Benefit to California (as written by the applicant)	California is home to the world's most cutting-edge stem cell research to advance biomedical therapies and improve the quality of life for those suffering from a wide variety of diseases. Yet, the infrastructure to safely deliver on-demand cell therapeutics is lagging behind. This proposal supports a critical value to Californians: calm and comfort from knowing their therapy can be stored, transported and delivered safely to their bedside in a time of need, with maximum therapeutic efficacy.
Funds Requested	$1,253,330
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

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	80
Lowest	55
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/RFA. Following the panel's discussion and scoring of the application, the 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 project have the necessary significance and potential for impact?
Yes: 7	• A better cryopreservant than DMSO would be good but I can't see how this works for whole cord blood and apheresis products. It would be much more useful for a single cell type product after GMP manufacture, eg., MSCs. • Yes, if superiority over established cryoprotective agents can be demonstrated.
No: 7	• A better short-term storage solution that lessened the need for specialty freezers could improve access to cell and gene therapies. However, there was not data that supported that objective. • From a manufacturing perspective, this holds little value for cell and gene therapy products as proposed. The current processes do not typically involve freezing the starting material. Cells/tissue are kept cold, not frozen, upon shipment to the manufacturer for further purification and cell expansion. • The project, as written, does not have the necessary potential for impact in the cell and gene therapy space. • Only demonstrating this product is as good as other products in the market is not impactful. The product should be better.
GWG Votes	**Is the rationale sound?**
Yes: 7	• Use of antifreeze proteins as DMSO replacement is based on an increasing body of literature.
No: 7	• Yes, for organs, but not for the utility of cell and gene therapy starting materials or the cell and gene therapy space. • A better cryopreservant than DMSO would be good, but for different interventions. • Even if used for whole blood, hospitals don't have the necessary freezers to allow this product to be used in the first place, even if effective. • Not convinced for the necessity of this product, especially because it is proposed for only cord blood and apheresis.
GWG Votes	**Is the project well planned and designed?**
Yes: 4	• The project has clear goals and can be completed in the proposed time frame. • Whether quality measures and tests to validate cell survival is sufficient needs to be confirmed by regulatory consultations.
No: 10	• The TPP needs to clearly lay out the goals for development. How long do they hope to show stability at -5C and at < -80C? They state long-term in 6 months but at the colder temperature range, longer times will need to be studied to be comparable or superior to DMSO. At -5C, a few weeks may be a significant advantage to current practice and may be the more attractive commercialization opportunity for this product. • I would expect to see well-designed stability studies with numerous characterization tests performed at multiple time points. • They would need to show cells were alive after 6 months at minimum. Why are they not targeting beyond this? • The short-term plans for stability need improvement. • I believe they need to identify and partner with a target therapeutic/company to advance this product meaningfully. Otherwise they are left diluting their effort in too many directions and not producing meaningful, necessary data. • It is unclear what impact this would have. • Unfocused.
GWG Votes	**Is the project feasible?**
Yes: 12	• Project is feasible, but does not seem important as proposed. • Underdeveloped milestones.
No:	• Not feasible for the cell and gene therapy space.

2	• Seems to be questionable.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 6	• A discussion of broader availability of organ transplants for underserved populations as a result of a longer shelf-life was provided. • Difficult to address this factor with the development of a cryoprotectant. • Limited information about how traditionally underserved communities may benefit.
No: 8	• Team built - how did they assure diversity of experience?

DIVERSITY, EQUITY, AND INCLUSION (DEI)

During the GWG discussion of the application, a GWG Board Member presented a critique and DEI score on whether the project upholds principles of diversity, equity and inclusion (DEI). DEI was discussed by the panel, and up to seven GWG Board Members provided final DEI scores and comments, shown in the table below. The responses were compiled and edited by CIRM for clarity.

DEI Score: 6

Up to 7 patient advocate and nurse 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.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	0	*none*
6-8: Responsive	2	• Good attempts to describe DEI value. • Do not seem to have intentional efforts to include diverse experience and thought in the hiring practices of their team.
3-5: Not fully responsive	1	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-14017
Title (as written by the applicant)	Gene Therapy for Alzheimer's Disease
Translational Candidate (as written by the applicant)	A targeted gene replacement therapy for Alzheimer's disease that contains the human PPT1 gene delivered in an AAV vector.
Area of Impact (as written by the applicant)	Alzheimer's disease (AD) in patients who are heterozygous for the PPT1 gene
Mechanism of Action (as written by the applicant)	Our product is a gene replacement therapy for a new gene target associated with AD. It will target Alzheimers' disease (AD) symptom onset in patients that are heterozygous for an AD-associated gene. It is anticipated that efficacy will potentially be long-term after a single dose, and may extend AD survival with significantly reduced disease progression.
Unmet Medical Need (as written by the applicant)	There is no therapy available for Alzheimer's disease (AD). The successful completion of this proposal could provide a targeted replacement gene therapy for a subset of over 100,000 AD patients.
Project Objective (as written by the applicant)	Hold IMPACT-CBER and pre-IND FDA briefing meetings
Major Proposed Activities (as written by the applicant)	• Non-GLP manufacture of a targeted gene therapy candidate for a subset of Alzheimer's disease patients. • Perform Alzheimer's disease efficacy testing in AD models for optimizing dosing regimens with downstream biomarker evaluations. • Conduct non-GLP safety evaluation with PK/PD biomarker supported data and hold FDA IMPACT-CBER pre-IND FDA briefing meetings.
Statement of Benefit to California (as written by the applicant)	The development of an effective treatment for Alzheimer's disease (AD) is clearly an important unmet need. The goal of this proposal is to perform pre-IND-enabling studies to translate a gene therapy into AD patients harboring a heterozygous mutation in a lysosomal enzyme gene. If successful, this could pave the way for similar treatments in AD patients containing heterozygous mutations in other lysosomal enzyme genes, and establish our team as a prosperous California-based commercial entity.
Funds Requested	$2,827,578
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

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/RFA. Following the panel's discussion and scoring of the application, the 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 project have the necessary significance and potential for impact?
Yes: 2	• Alzheimer's disease (AD) represents a major health burden. There is a significant need for new therapies in this space.
No: 13	• The applicant is developing targeted gene therapies that could be used within the context of severe neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's Disease (PD). • Neurodegenerative diseases, such as AD, are increasing in prevalence and represent a significant health burden. • The prevalence of this gene defect and the link between heterozygosity and outcome are both unclear. Are there data showing that the genotype is prospectively predictive of AD? • While there is a high unmet need for Alzheimers there is insufficient evidence that gene therapy targeting PPT1 would have a sufficient risk/benefit ratio. • The impact will be delayed considerably by the need for clinical history studies to validate the applicant's hypotheses. • The relevance of PPT1 heterozygosity in AD and PD is unclear. • The study is based on a mouse model with no clear link to clinical reality. • The current data do not support development of the proposed product. • The current application has limited significance and impact.
GWG Votes	**Is the rationale sound?**
Yes: 0	*none*
No: 15	• There is no clear mechanistic reason why heterozygous deleterious variants of PPT1 lead to Alzheimer's disease. There is no clear functional relationship. Also, no natural history data or other data, beyond Table 1, that shows a clear link between the presence of these heterozygous deleterious variants and the causation of AD. • It is not clear what proportion of AD patients actually have PPT1 heterozygosity, nor is it clear when treatment would need to be applied to be meaningful, nor is there a discussion of what a clinical trial would look like. • The hypothesis is intriguing and potentially disruptive for the field, but there is no natural history data that provides convincing evidence linking the proposed mutation and the development of AD. • My concerns revolve around weak hypothesis testing and likelihood that the animal model is not indicative of actual AD contributed to potentially by PTT1 genetics. • What is the relevance of the mouse model endpoints? • Human genetics data is a minimal requirement to estimate the relevance of PPT1 heterozygosity in AD/PD. • Rationale is weak.
GWG Votes	**Is the project well planned and designed?**
Yes: 1	*none*
No: 14	• There are deficiencies in the proposal, ranging from the difficulty of developing a therapy for an uncharacterized subset of patients to limited consideration of how the proposed treatment would be applied. • The overall plan seems reasonable. However, the planned studies fail to address the basic limitation of the overall rationale for developing the proposed drug product. • The project plan lacks clarity around how to find AD patients with PPT1 heterozygosity, or how many to study. • A more stepwise approach is needed for establishing toxicology time courses and dose responses in pilot trials of route, BD and PD durability. • Toxicology studies should address the effects of overexpression of PTT1 as well as pharmacologic toxicology of chronic overexpression. • Could the therapy trigger an immune response to PTT1? • The manufacturing section is inadequate.

	• The project will not lead to a well-informed pre-IND package.
GWG Votes	**Is the project feasible?**
Yes: 3	• Yes, but underdeveloped to meet the CIRM TRAN program objectives.
No: 12	• It will takes years of pre-program research to solidify causality and support the potential sufficiency of this approach to treatment. • The overall program is far from proof-of-concept. • It's uncertain the starting hypothesis is true. • The contingency plan is limited. There are no contingencies for things like the lack of non-human primates (NHPs) due to current supply shortages, which could lead to significant delays in this type of program. Also, the proposal does not include contingencies for manufacturing. • The technical aspects of the work are certainly feasible, but the results may not be relevant to progression to a clinical trial.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 8	• The applicant attempts to address DEI, but the project is very early stage. • The unmet need is well described, as is the impact of AD on underserved communities. • No engagement of underserved or disproportionately affected communities is currently planned.
No: 7	• Intracerebral injections are not easy to administer. Also, the population with this heterozygous genotype might not be spread across multiple groups. • The authors provide a fairly superficial plan to address and account for the influence of race, ethnicity, sex, and gender diversity in their proposed clinical trial.

DIVERSITY, EQUITY, AND INCLUSION (DEI)

During the GWG discussion of the application, a GWG Board Member presented a critique and DEI score on whether the project upholds principles of diversity, equity and inclusion (DEI). DEI was discussed by the panel, and up to seven GWG Board Members provided final DEI scores and comments, shown in the table below. The responses were compiled and edited by CIRM for clarity.

DEI Score: 7

Up to 7 patient advocate and nurse 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.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	0	*none*
6-8: Responsive	3	• Impact on underserved communities is not well-described. No engagement of communities impacted is described.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN3-14026
Title (as written by the applicant)	Optimizing Cell Therapy Delivery: Developing a Novel Device Designed to Protect Cells During Infusion
Translational Candidate (as written by the applicant)	The candidate to be studied is a novel cell infusion device which improves post-infusion cell viability and functionality of a cell-based therapy.
Area of Impact (as written by the applicant)	This novel cell infusion device improves cell therapy efficacy by increasing cell functionality and quality post-infusion.
Mechanism of Action (as written by the applicant)	This novel cell infusion device works by reducing damaging mechanical forces applied to cells during targeted cell therapy delivery. Cells are notoriously sensitive to their mechanical environment, and off-the-shelf delivery systems have been shown to damage, alter, and kill substantial percentages of infused cells. This device incorporates several key innovations into a familiar syringe-type infusion system in order to limit those damaging mechanical forces and improve cell therapy delivery.
Unmet Medical Need (as written by the applicant)	The potential of cell therapy for regenerative medicine is massive, but these applications require targeted delivery of cells. Currently available devices damage and kill cells during infusion; there is a vital need for devices that allow accurate delivery while keeping cells alive and functional.
Project Objective (as written by the applicant)	Pre-submission meeting with FDA for 510(k)
Major Proposed Activities (as written by the applicant)	• Evaluation and definition of clinical user needs and intended uses. Implementation of a quality management system, design control, design history file, and risk management systems. • Optimization of prototype device and testing of technical performance and determination of regulatory and clinical path. • Design verification and validation readiness and completion of pre-submission meeting with the FDA.
Statement of Benefit to California (as written by the applicant)	Hundreds of thousands of patients in California suffer from advanced kidney and liver disease, for which the treatment options are limited. Cell therapy offers a promising new treatment option for these and many other diseases, yet better devices are required for successful clinical translation. The benefits to the state of California include: better prognosis for patients, reduction in health care costs, and maintaining California's prominence in stem cell research.
Funds Requested	$685,267
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

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/RFA. Following the panel's discussion and scoring of the application, the 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 project have the necessary significance and potential for impact?
Yes: 1	• Yes, delivery of stems cells are not adequately performed by current devices.
No: 14	• No. What good evidence is there that cells are damaged by existing techniques or that this will change the efficacy of MSCs? • Better delivery of cells may ultimately help to improve efficacy, however, for many cell therapy applications, especially MSCs, the challenge is most likely not delivery, but their general potency. • How this addresses unmet medical need was not shown. • While I can see that improving cell delivery might have some impact I do not see it as the difference between efficacy and a failed study. • There is no data that supports a 25% reduction in viability of delivered cells can lead to treatment failure. • I think the reason the MSC clinical trials fail is because these cells have only mild immunomodulatory and anti-inflammatory properties which is not enough to be impactful in a clinical setting. Normally MSCs are given in an allogeneic setting and so the cells are quite transient with most cells disappearing after 48-72 hours.
GWG Votes	**Is the rationale sound?**
Yes: 0	• Unmet need and strategies for solving needs are supported by literature review. • The "anti-cell adhesion coating applied to the fluid contacting surfaces of the delivery device to prevent adherent cells from attaching and optimizations to the flow characteristics for a reduction in cell clumping" is completely uncharacterized in the application. They clarified that they plan to test with several different commercially available coatings.
No: 15	• The rationale is that current methods to deliver cell therapies have been developed for small molecules or macromolecules such as protein therapeutics. Improvement in cell delivery might have some small impact on efficacy of a cell therapy product which could be valuable under some circumstances. • The data supplied in the application is quite scant. There are really no details in the examples given. Figure 5 for instance purports to show an increase in viability and functionality of MSCs when their device is used. The figure legend states the experiments were performed 3 times. Why are there no error bars on the histograms? The table states that the experiment was analyzed at 1, 3 and 7 days post-infusion. Where is the data from each day post-infusion? What does the data in the histogram represent? What were the cells infused into? What media was used for the cells both before and after infusion? How were the cells maintained before and after infusion? What is the source of the MSCs? What is the evidence that the cytokine measured is a measure of functionality? Were any other cytokines looked at? • The same questions about viability also apply to the "macrophage-like cells" in figure 6. What exactly are "macrophage-like cells"? • Background data about MSCs and "macrophage-like cells" are not convincing. • What is the data that shows that increasing cell viability by 25% will increase efficacy? Why couldn't one just increase cell dose given that most MSCs die or at least disappear within a few days of transplantation? • Without a clear disease target and principle preclinical proof of concept it is difficult to find a measure that would allow for an evaluation of effect-level increase by improved delivery. • Stating that "the literature clearly shows" requires more elaboration of the specific literature that supports the study rationale.
GWG Votes	**Is the project well planned and designed?**

Yes: 0	• Current delivery systems are not adequate for intra-arterial/direct cell administration.
No: 15	• Further work needs to be done to demonstrate that cell delivery is an issue with respect to the efficacy of a cell therapy product. • The project is based on an unproven premise that cell delivery is a crucial problem which impacts efficacy of delivered cells. • A focus on an organ and specific disease would help. • I was disappointed that the details of the device and the ways that the prototype will be altered to achieve an optimal device were very scant. A schematic of the device is needed. • There is a patent application filed but it is not yet public and we cannot see the details in the patent application. • There is a suggestion that the team will evaluate different materials in the pressure chamber and for decreased adhesion inside the device, but no information about what options will be considered. • For an engineering application, I would expect to have some information regarding the design considerations in addition to the aims. • No info on the design/development considerations or how they will improve the prototype.
GWG Votes	**Is the project feasible?**
Yes: 5	• Yes, I think the project would be feasible in the timeline outlined. • I think there needs to be a lot more explanation of current data and a nexus between the improvements and efficacy established.
No: 10	• The feasibility is unclear. There are no details of what is being done. • Unclear without designs.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 10	• The application acknowledges the disparity in treatment access for late-stage liver disease as well as a disparity in kidney disease incidences for underserved communities that a device to improve cell therapy efficacy may help. • The application suggests the company will consider sex as a biological variable in preclinical and animal trials but no animal trials are proposed in the study. • The team will recruit two interns from underserved community colleges to the product development team. • Yes, page 33 details how they will account for DEI issues. • Not a very robust DEI discussion, but they do intend to have internal DEI training but no indication of how this will translate into their project. Some discussion of underserved communities, again not very robust.
No: 5	• Not enough details are provided.

DIVERSITY, EQUITY, AND INCLUSION (DEI)

During the GWG discussion of the application, a GWG Board Member presented a critique and DEI score on whether the project upholds principles of diversity, equity and inclusion (DEI). DEI was discussed by the panel, and up to seven GWG Board Members provided final DEI scores and comments, shown in the table below. The responses were compiled and edited by CIRM for clarity.

DEI Score: 6

Up to 7 patient advocate and nurse 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.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	0	*none*
6-8: Responsive	3	• Internal DEI training is described.

		• Some description of impact on underserved communities.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*