APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Resubmission	Previous CIRM Funding	Disease Indication	Product Type	Approach
TRAN1-14698	Hematopoietic Stem Cell Gene Therapy for Wiskott Aldrich Syndrome	**$3,999,899**	**Y**	**95**	95	2	92	99	13	0	N	N	Wiskott Aldrich Syndrome	Cell and gene therapy	Development of a gene therapy that provides a functional WAS gene in HSC for transplant.
TRAN1-14671	Development of Autologous Cell Replacement Therapy for Parkinson's Disease: Path to Personalized Treatment	**$3,841,110**	**Y**	**90**	92	3	90	95	13	0	N	N	Parkinson's disease	Cell therapy	Development of an autologous iPSC-derived dopaminergic progenitor cell therapy for transplant.
TRAN1-14625	Hematopoietic Stem/Progenitor Cell-Based Chimeric Antigen Receptor Gene Therapy for HIV Infection	**$6,140,723**	**Y**	**90**	91	2	88	95	13	0	N	Y	HIV/AIDS	Cell and gene therapy	Development of a chimeric antigen receptor in HSC that will mature into T, NK and other immune cells targeting HIV.
TRAN1-14716	Targeting multiple myeloma (MM) with BCMA CAR NK cells expressing a targeted bispecific antibody	**$6,036,001**	**Y**	**90**	90	2	88	95	14	0	N	N	Multiple myeloma	Cell and gene therapy	Development of a chimeric antigen receptor in NK cells that targets multiple myeloma.
TRAN1-14613	Novel T cell immunotherapy for lung cancer	**$5,689,540**	**Y**	**90**	89	3	80	90	12	1	N	N	Lung cancer	Cell and gene therapy	Development of an autologous T cell receptor immunotherapy that targets lung cancer cells.
TRAN1-14623	Telomerase mRNA for short telomere related pulmonary fibrosis	**$3,984,942**	**Y**	**90**	89	2	86	92	11	0	Y	N	Idiopathic pulmonary fibrosis	mRNA therapy	mRNA encoding factor delivered via a lung-targeting lipid nanoparticle to extend telomeres in diseased lung cells.
TRAN1-14062	Escape-Resistant Oligonucleotide Therapy (ONT) for Cytomegalovirus (CMV) Disease in Hematopoietic Stem-Cell and Solid-Organ Transplant Patients	**$3,977,180**	**Y**	**88**	88	2	85	90	11	0	N	N	CMV infection	Oligonucleotide therapy	Development of an oligonucletide therapy that kills CMV-infected cells.
TRAN1-14609	Enhanced Autologous Pancreatic Islet Transplantation and Survival for Diabetes Mellitus Therapy	**$6,056,713**	**Y**	**88**	86	6	70	95	11	2	N	N	Diabetes	Cell therapy	Development of small clusters of pancreatic islet cells for transplantation.
TRAN1-14649	Extracellular Vesicle-Based Therapy for Corneal Scars	**$5,779,276**	**Y**	**85**	81	11	50	92	7	6	N	N	Corneal scars	Biologic	Development of an extracellular vesicle therapy derived from corneal stromal cells to treat corneal scars.
TRAN1-14710	AAV Gene Therapy for Treating Congenital Hereditary Endothelial Dystrophy (CHED) associated with Biallelic SLC4A11 Mutations	**$4,338,166**	**N**	**80**	80	6	70	90	5*	8	N	N			
TRAN1-14620	Development of a Gene Therapy for the Treatment of Arginase Deficiency - Translating from Proof of Concept to Pre-IND Meeting	**$4,771,122**	**N**	**80**	80	5	70	90	2	11	N	N			
TRAN4-14726	Development of a low-cost, clinical-grade iPS maintenance medium for enabling stem cell therapy manufacturing	**$999,848**	**N**	**80**	79	9	55	90	5*	9	N	N			
TRAN1-14714	Noncoding RNA drug TY1 as a therapeutic candidate for scleroderma and systemic sclerosis	**$2,796,329**	**N**	**75**	74	10	55	85	3	10	N	Y			
TRAN1-14688	High-titer bifunctional lentiviral vector to reduce costs and increase access for Sickle Cell Disease gene therapy	**$3,580,750**	**N**	**70**	71	7	60	80	0	13	Y	N			
TRAN1-14692	Mature iPSC-Derived β Cell Spheroids for Treating Induced Type I Diabetes	**$5,400,000**	**N**	**70**	70	8	50	85	1	12	N	N			
TRAN3-14646	Clinical translation of MPI for cellular imaging of CAR T cells	**$1,984,740**	**N**	**65**	67	9	50	85	1	12	Y	Y			
TRAN1-14629	Neurogenic hydrogel stimulation of stem cells to regenerate radiation-damaged salivary glands	**$2,384,806**	**N**	**65**	63	6	50	70	0	13	N	N			
TRAN3-14626	Optimizing Cell Therapy: Developing a Novel Delivery Device Designed to Improve Cell Therapy Efficacy	**$497,063**	**N**	**-**	-	-	-	-	0	13	Y	N			

* Qualify for Minority Report

Application #	TRAN1-14698
Title (as written by the applicant)	Hematopoietic Stem Cell Gene Therapy for Wiskott Aldrich Syndrome
Translational Candidate (as written by the applicant)	Human hematopoietic stem cells that have been modified to express a functional WAS gene to treat patients with Wiskott Aldrich Syndrome (WAS)
Area of Impact (as written by the applicant)	These studies will bring stem cell gene therapy for WAS closer to the clinic especially for those without an HLA match or disease too severe for hematopoietic stem cell transplantation (HSCT)
Mechanism of Action (as written by the applicant)	Hematopoietic stem cells (HSCs) with defective WAS protein (WASp) expression are modified with a lentiviral vector which restores a normal copy of the defective gene. Transplantation of gene-modified HSCs, which are self-renewing and long-lived, produce all blood lineages, including white blood cells and platelets which can correct the severe autoimmunity, immunodeficiency, and bleeding episodes present in WAS.
Unmet Medical Need (as written by the applicant)	There is no curative treatment for WAS patients without a bone marrow match. Gene corrected HSC can cure WAS and provides a therapeutic option for these patients. This proposal will advance the field of stem cell gene therapy and treatment of primary immune disorders.
Project Objective (as written by the applicant)	Conduct a successful Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Obtain clinical grade lentiviral vector and demonstrate the ability to manufacture the stem cell product at clinical scale • Perform rodent studies to assess safety and the effective dosage of the cell product • Prepare Pre-IND package. Complete Pre-IND meeting with the FDA.
Statement of Benefit to California (as written by the applicant)	Safe, definitive therapies for Wiskott Aldrich Syndrome represent an unmet medical need. Allogeneic stem cell transplant is frequently complicated by graft-versus-host disease or limited by lack of HLA matched donors. Successful demonstration that stem cell gene therapy can safely and effectively cure WAS will shift the paradigm by which patients will be treated and provide a foundation by which other immune and blood diseases may be cured in the future.
Funds Requested	$3,999,899
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: 95

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	95
Median	95
Standard Deviation	2
Highest	99
Lowest	92
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/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	• Wiscott-Aldrich Syndrome (WAS) is a primary immunodeficiency disorder. The current standard of care is via allogeneic hematopoietic stem cell transplant (HSCT). However, this approach has limitations, including lack of available matched donors, graft versus host disease (GvHD), and toxicity due to the myeloablative regimen used in preparation for the transplant. Patients without a matched donor have a median age of survival of 25 years. Genetically-modified (lentiviral vector-based) autologous HSCT has been explored as an alternative to allogeneic HSCT. While clinical results are overall very positive and promising with restoration of most markers of immune function and clinical evidence of benefit, there is a challenge with full restoration of platelet counts and clotting function to varying degrees. The aim of the proposed product is to use a modified vector carrying noncoding regulatory elements in the hopes of gaining full restoration of platelet counts and function. Therefore, if this approach were to work, it would be a superior option to any other available options, in particular in patients who do not have available matched donors for allogeneic HSCT. If successful, this could be an improvement over allogeneic HSCT due to the use of a less toxic myeloreductive regimen, and no risk of GvHD. • WAS is a rare disease with no current autologous genetic therapy approved. The only curative, therapeutic modality is an allogeneic hematopoietic cell transplant, which is limited in availability due to the lack of suitable matched donors. Thus this project, by developing an autologous therapy, definitely addresses an unmet need. • WAS is a disease with unmet medical need. Curative therapies are sought due to the morbidity and mortality of this disease. • The bioinformatically identified regulatory element integrated into the lentiviral vector to increase platelet production is a novel feature which is clinically relevant and overcomes a limitation in the field. If successful, this product has the potential to accelerate the access to a viable genetic therapy for WAS. • The increased production of platelet counts is a value proposition that is missing in many other genetically modified products. • The proposed novel construct should allow potential treatment of many more patients with the disease. • The current standard of care with allogeneic transplant has limitations and this approach would present significant advancements. • The proposed drug product is an autologous gene-modified cell therapy for the potential curative treatment of a rare X-linked disease, WAS. • The proposed product would significantly improve the current standard of care. • The proposed product would be beneficial for both patients and healthcare providers.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• The project is based on the observation that the WAS gene-derived sequences used in in prior lentiviral vector-based HPSC clinical trials were insufficient to obtain full restoration of platelet numbers and function. The applicants have identified novel non-coding sequences and demonstrate correction of thrombocytopenia in a mouse model. • The applicants have a strong body of data that they have developed to support their approach, starting from screening and moving through mouse studies which compare their sequence to sequences used in prior clinical trials. In these studies, the applicants' vector shows significantly increased levels of WASp in all lineages, including platelets. The safety profile is the same for both vectors in a clonogenic assay. • The rationale is based on previous successful development of therapies for genetic disorders. • The pre-clinical information is sufficient and supports the further development of this product. • The application includes excellent preclinical validation of the lentiviral construct to support higher platelet production. • The proposed transgene construct provides the potential for advanced care.

	• This LV-based technique is based on proven successful science. • The data provided indicates that this treatment should be successful. • The data indicate that further drug product development is warranted.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 13	• Lentiviral vector manufacturing will be through a vendor with approved Biologics License Applications based on this technology. This translates into a high likelihood of success for the vectors to be manufactured in compliance with FDA's recommendations for phase 1 and throughout development. • The applicants have a detailed set of lot release criteria developed for the vector that are aligned well with what FDA will be seeking in the phase 1 review. Their cell processing plan, in-process, and final product testing plans are well-considered and address FDA recommendations. • The plan is well-thought out and provided sufficient information to support successful regulatory agency interactions for the commercial development of the product. • From a CMC perspective, this project is very well planned and the activities are appropriate to advance the development of the drug product. • The CMC plans are focused on the quality and safety of the starting materials and final drug product. The CMC program is very well designed for success. • The CMC plans including the timing of activities are designed with quality and urgency. • The applicants have detailed, well-considered lot release criteria for the vector and transduced cells. However, the organizational chart doesn't indicate any quality infrastructure. This could be mitigated by the planned use of contract organizations with extensive experience in doing GLP studies and GMP manufacturing. • The applicant organization has a solid pipeline for the development of such products.
No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 13	• This project is feasible because the applicants have the proposed activities distributed to various contractors, and each of these is not inter-dependent on another. There are key elements that are dependent on the outcome of the first year of work, and have a high likelihood of success to be able to be completed within the expected time frame, as long as all the pieces of year 1 are completed as anticipated. • Yes, there is built in redundancy to support the successful advancement of the project according to the milestones. • The applicants have assembled a team of highly experienced and qualified individuals, with decades of experience. They have a high likelihood of success with the team they've assembled.. • The data presented in the proposal and the experience of the team and contractors support feasibility. • The proposal is well positioned to result in successful CMC manufacturing. • Most notably from a CMC perspective, there is a CMC consultant in place to support to successful generation of starting materials and final drug product.
No: 0	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13	• This product has the potential to significantly address issues of disparity quite directly, given that only 40% of individuals with WAS from Asian and White Hispanic descent, and <25% of individuals of African descent, are likely to find a matched unrelated donor for HSCT (compared to 75% of individuals of European descent). • The team has considered these issues, and has developed a recruitment strategy that reflects the diverse patient population of California, tapping into a variety of organizations and networks to both reach WAS patients and those of under-represented groups. Further they note that California's Children Services has been authorizing use of gene therapies in individuals without access to sufficient health care insurance coverage. • They are working closely with the head of the Wiscott-Aldrich Foundation and will participate in a patient-focused drug development session led by FDA. • The plan is very well designed to approach issues of race and ethnicity. The disease in question only affects males.

	• The outcomes would advance the unmet medical needs of California not just for this particular illness but by extension for similar illnesses that disproportionately impact diverse populations. • The proposal specifically names groups that will be consulted in the development of DEI plans. • The proposed DEI plan is very thorough.
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	• The applicant's approach goes beyond typical expectations for DEI.
		• This proposal seems to take the DEI issues very seriously in a variety of different ways. Especially impressive was the manner in which the applicants outlined the challenges related to DEI and their approach to meeting the challenges:
		  • They begin by pointing out that the existing treatments for WAS are not available to non-European populations for a variety of reasons including late and misdiagnosis of diseases of immunodeficiency and the lack of matched donors, especially for African-Americans but also including Asians and Hispanics. The applicants suggest a solution of working with advocacy groups to advance universal newborn screening for such diseases.
		  • They have a very robust outreach plan including 47 centers specializing in treating rare immunodeficiency diseases. They also have highly commendable recruitment goals set for a small population addressing DEI.
		  • They are very concerned with patient costs and are working to make this illness covered for all patients. In their studies, they are planning to cover all patient costs including treatment and transportation for the eventual trial patients.
		  • Finally, they plan to work with patients and family groups to gain input about safety concerns. Although they believe their product will be very safe, the applicants understand that families have grave concerns related to harm done by other previous treatments.

6-8: Responsive	1	• The DEI approach seems appropriate at this time.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-14671
Title (as written by the applicant)	Development of Autologous Cell Replacement Therapy for Parkinson's Disease: Path to Personalized Treatment
Translational Candidate (as written by the applicant)	Autologous iPSC-derived dopaminergic progenitor cells
Area of Impact (as written by the applicant)	Parkinson's Disease
Mechanism of Action (as written by the applicant)	Autologous iPSC-derived dopaminergic progenitor cells represent a promising strategy to replace the nigrostriatal cells which are lost in Parkinson's Disease (PD). While approaches using fetal tissue / allogeneic stem cells show great promise, they are not sufficiently personalized to provide maximal safety and efficacy to the broadest demographic of PD patients. If successful, this cell replacement therapy could dramatically improve the standard of care and prognosis for PD patients.
Unmet Medical Need (as written by the applicant)	Current medicines for PD only address the symptoms of the disease by boosting dopamine production from nigrostriatal neurons which continue to degenerate. The proposed approach will replace the degenerating neurons and in this way slow, halt, or even reverse the progression of the disease.
Project Objective (as written by the applicant)	Pre-IND meeting; GMP-ready processes
Major Proposed Activities (as written by the applicant)	• collect tissue samples, generate iPSC, and produce dopaminergic neurons from several PD patient and healthy volunteer donors • assess the reliability and iteratively improve processes for manufacture and QC of autologous replacement cells to apply to all PD patients • perform animal studies and complete the data package to submit to the FDA for a Pre-IND meeting
Statement of Benefit to California (as written by the applicant)	Currently Parkinson's disease afflicts approximately 100,000 Californians, exacting tremendous economic and emotional tolls on individuals and society. A disease-modifying personalized cell replacement therapy for PD would improve this situation dramatically, for our families, and at a socioeconomic health system level. The state may save hundreds of millions of dollars in healthcare costs per year.
Funds Requested	$3,841,110
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	92
Median	90
Standard Deviation	3
Highest	95
Lowest	90
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/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 project is aimed at treating Parkinson's disease (PD) patients using autologously derived dopaminergic precursor cells derived from multiple iPSC lines. At present there is no cure for PD. The current standard of care revolves around treating symptoms. In general, PD patients deteriorate over time. • There are currently only symptomatic therapies available and no cures or restorative treatments for Parkinson's disease. The use of an autologous iPSC therapy for the treatment of sporadic Parkinson's patients is necessary. This program has the potential to meet the criteria for a pre-IND. • Yes. The project seeks to develop autologous cell therapy for Parkinon's Disease. There are currently only symptomatic therapies available and no cures or restorative treatments. • Better treatments for Parkinson's disease are important for individual patients, caregivers, and public health. • Given the lack of a current curative treatment for PD and the fact that the product envisioned in this application is autologous (which may have advantages over an allogeneic product), this product, if successful, could address a large unmet medical need. • There are other cell therapies in clinical trials for PD that are focused on allogeneic products, but this project is focused on autologous products. • The novelty of this product is that it is autologous and may be more focused on A9 midbrain progenitors. This project does increase the likelihood of developing a novel product that improves patient care. • The applicants provide evidence that an autologous product may be superior to an allogeneic product. From that perspective the product could be impactful. The value proposition is difficult to quantitate as autologous products by their very nature are expensive to produce. • Yes, the product is autologous which means there is no need for immune suppression.
No: 0	*none*
GWG Votes	**Is the rationale sound?**

Yes: 13	• The use of autologous iPSCs may be an advantage to mitigate some of the potential challenges with allogeneic iPSCs. This will mean more donor variability to confirm consistency of the Drug Product.
	• The project has 3 defining scientific rationales which are sound:
	  ◦ Firstly there is inherent variability in iPSCs generated from the same cell source. The applicants intend to isolate multiple cell lines from each PD patient as well as normal healthy volunteers to account for this variability. In total they intend to isolate many independent iPSC lines and test them in vitro.
	  ◦ Secondly, the differentiation protocol developed by the applicants and their collaborators is a refinement of previous protocols whereby several morphogens are titrated and the timing of their application is modulated so that the differentiation is more homogenous and contains more mid-brain A9 dopaminergic progenitors and less hindbrain fated cells.
	  ◦ Thirdly, the applicants have generated in vivo data to show there is better survival and outcomes with an autologous cell product compared to an allogeneic cell product.
	• The project is based on a sound scientific rational in most aspects and evidence from fetal tissue trials as well as currently ongoing stem cell trials. The ultimate patient group to which this treatment can be applied could be more clear.
	• Overall, the scientific rationale is robust and well-researched. The potential to implant iPSCs into the relevant regions proved feasible in rats and large animal studies. The clinical approach has been tested previously and appears safe. A deeper assessment of functional outcomes in large animals would have been preferred, but this should be feasible based on the translational plan.

	• The data, particularly the functional data in large animals, supports the development of the product. The data are very clear that over time the autologous cells outperform allogeneic cells. • The application includes strong supporting preclinical data.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 13	• The proposal outlines specific tasks that will lead to an interaction with the FDA. • The applicants have a good plan to generate data to support a pre-IND meeting with FDA. • This program is well thought out and anticipates future requirements after the pre-IND meeting. • The applicants indicate a clear understanding of preclinical studies and manufacturing expectations to support a pre-IND. • The project holds a high scientific standard and translational efforts are good, but it may be a bit optimistic that it will result in a pre-IND. • Developing cells lines from both PD patients and normal healthy volunteers will control for differences in the source of the cell line. • Deriving multiple cell lines from each subject is prudent. This allows testing of cell lines for genetic stability and differentiation capability. • The refined differentiation protocol will allow a more homogenous population of target cells to be produced. • The differentiation protocol is very advanced. • Extensive animal testing will show functional capacity of the cell product. • The program is of high quality in terms of cells, animal models and methodology. • Establishing proof-of-concept in two species indicates strong feasibility of the scientific rationale. The studies were well-designed and controlled. • The application is very well written and is a pleasure to read. The applicants have thought through the potential pitfalls that may occur along the way (things like genetic instability of an individual cell line) and have accounted for that. • An institution related to the applicant institution is constructing a GMP facility which will be completed in a timely manner for engineering runs (to provide product for definitive pre-clinical studies) and clinical product for use in the clinic.
No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 13	• The applicants are very well qualified. This is an experienced team who have been involved in a number of cell therapy projects, some of which are in the clinic. • The team does have the resources to conduct these activities. In addition the construction of a GMP facility is proceeding ahead of schedule and will provide a resource to produce product for definitive pre-clinical and clinical testing. • The risks have been thought through and the contingency plans are reasonable and appropriate. • The timelines are ambitious but reasonable given the knowledge and expertise the applicants already possess. • The project is very ambitious but performed by a very qualified team. • The plan to generate cGMP grade for pivotal GLP toxicology and first-in-human studies appears timely and robust. The staff involved in the development plan appears to be appropriate. • One concern is the route of administration and the dosage regimen. The duration of the treatment will be an important factor in the practical acceptance of the proposed therapy.
No: 0	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13	• The proposal adequately describes the implementation of the principles of DEI for this stage of the program. • The DEI section of the grant appears to account for the influence of diversity of race, ethnicity and gender. The applicants intend to isolate cell lines from diverse individuals. Given the small sample size, it would be hard to incorporate robust diversity for this project but the applicants will more fully address these issues as a product is developed. • Fibroblasts from diverse donors and both sexes will be used from start.
No:	*none*

0	

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

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	• Patient selection criteria appears unbiased. The development of a DEI committee is commendable.
6-8: Responsive	2	• The application includes good demographic data and well-thought out research approach.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-14625
Title (as written by the applicant)	Hematopoietic Stem/Progenitor Cell-Based Chimeric Antigen Receptor Gene Therapy for HIV Infection
Translational Candidate (as written by the applicant)	A blood forming stem cell based therapy to treat HIV infection and enhance HIV immunity.
Area of Impact (as written by the applicant)	We are seeking to develop a therapy to treat HIV infection to replace standard drug therapy and cure people of the virus.
Mechanism of Action (as written by the applicant)	We are seeking to develop a gene therapy that modifies a HIV infected individual's immune system to directly attack HIV infected cells in a better way than would occur naturally and also protect these modified cells from being infected themselves. Through the enhancement of these immune responses, we are attempting to provide a way for HIV to be cleared from the body.
Unmet Medical Need (as written by the applicant)	HIV infection remains a top public health concern worldwide and, though it can be managed with therapy, there is no curative treatment that is available for all. An improved means to eradicate HIV in every infected individual is needed.
Project Objective (as written by the applicant)	Our goal is to have pre-IND meeting with the FDA.
Major Proposed Activities (as written by the applicant)	• We will establish Good Manufacturing Practice (GMP) processes for gene therapy vector production and cell product manufacturing. • We will develop assays and perform preclinical safety and pharmacology studies to identify dosing and efficacy in humanized mice. • We will prepare clinical and regulatory protocols towards approval for further IND and clinical trial development.
Statement of Benefit to California (as written by the applicant)	California ranks second in the nation in cases of HIV, with over 170,000 persons currently living with HIV with the direct healthcare cost to California approaching $1.8 billion annually. A curative treatment is therefore a high priority. A stem cell based therapy offers promise for this goal, by providing an inexhaustible source of protected, HIV specific immune cells that would provide constant surveillance and potential eradication of the virus in the body.
Funds Requested	$6,140,723
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	91
Median	90
Standard Deviation	2
Highest	95
Lowest	88
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/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	• Development of a cure or functional HIV remission is a major priority. Currently, almost 40 million people are living with HIV worldwide, and approximately 135,000 are living in California with approximately 4,000 newly diagnosed in California each year. People living with HIV (PLWH) must take antiretroviral therapy for life in order to suppress the virus. The medications are costly, require strict adherence to remain effective, and have side effects. A therapy that allowed PLWH to thrive in the absence of antiretroviral medications would be highly beneficial in terms of decreased toxicities and expenses and improved quality of life. • While people living with HIV can maintain low viral loads and good quality of life with combination antiretroviral therapies (ART), there is still a quest for ways to find a "functional" cure these individuals, whereby viral rebound can be controlled without giving rise to symptoms. Current risks still include development of viral mutations that give rise to resistance, rebound on stopping therapy, as well as adverse effects of the various antiviral drugs. Therefore, finding a full cure is still a high priority in the field of HIV research. The strategy being developed by this team has yielded promising data from preliminary studies that suggests the development of autologous hematopoietic stem cells carrying their specific modification of a CAR may provide a path towards a full cure. • The value proposition here is a full withdrawal of ART and cure of HIV. • Clearly addresses an unmet medical need to not only improve the quality of life, i.e., reduce the burden of chronic drug therapy, but also may have potential to result in a cure. • The product offers a different modality for treatment of HIV. • The unmet medical need is the absence of a cure for chronic HIV infection. • The product is based on stem cell technology. It involves gene modification of hematopoietic stem/progenitor cells (HSPC) with vectors carrying CAR transgene. The approach has curative potential in the control of HIV infection. • This stem cell technology is innovative in numerous ways and potentially could be applied not just in HIV, but other areas of medicine as well such as other chronic infections (e.g., hepatitis B) and malignancies. The remarkable persistence of transduced cells seen in the large animal model as well as the circulation of these cells to key sites of HIV reservoirs, e.g., CNS, secondary lymphoid tissues, is a major strength over current CAR T cell approaches in which transduced peripheral blood T cells fail to persist. • Although the current approach is costly, once the proof of principle is established it could be modified to create the same product more efficiently, perhaps without even requiring cells to be removed from the individual.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• The rationale is sound. Preliminary data support the rationale and further development. • Great supporting preclinical data that support wider biodistribution and longer cell persistence than current T cell programs • There are clear data indicating that virus-specific T cells mediate important control of HIV replication in vivo. • Robust data are presented to demonstrate that stem cells can be modified to express virus-specific CARs, that the CAR cells exert antiviral activity, and that they traffic to and persist in appropriate compartments of the body including germinal centers, gut and cerebrospinal fluid where the virus resides. • Yes, the team is building on the body of knowledge and experience in CAR-T cells. As they note, the use of HSPC-modified cells that carry the HIV-specific CAR provides advantages over infusion of CAR-modified T cells: the cells are educated in the thymus as they mature into T-cells and engraftment of CAR-modified HSPC means that there's a life-long reservoir of these cells that can mature into T cells and protect the individual from infection and spread of HIV as it becomes reactivated from various reservoirs. In

	addition, the investigators have learned from prior experience that the T cells must also be armed with an active antiviral in addition to the CAR, and so they've also incorporated a modification that prevents viral fusion with the host cell membrane, thus defending the CAR-T from HIV infection. Further they've modified the cells to allow for HSPC differentiation into mature T cells. • Antiviral activity demonstrated in mice and the large animal model is somewhat modest, but nonetheless present. It is quite possible that antiviral activity will be more robust in humans with an intact immune system that will collaborate with the CAR T cells in suppressing HIV replication. • Risks include potential off target effects of gene therapy and immune effects of myeloablation. These will need to be monitored, but currently the potential benefits are believed to outweigh the risks. • Development of the animal models that may mimic human disease and the possibility of off-target toxicities should be considered in conjunction with a nonclinical consultant. • Some concerns on novel inclusion of a modification to reduce virus infection of cells should allow for persistence. An assay to demonstrate expression should be given attention.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 13	• The project is well-planned. • Proposed preclinical studies are well thought out. • The project is laid out in a very logical systematic way with 6 clear milestones. There are very thorough considerations of potential problems and alternative approaches. • The product development for the proposed research studies is well-defined. Persistence of the effect should be tested if possible in an animal model. • The manufacturing information will need more detail to be pre-IND ready, including detailed SOP and batch records, along with lot release criteria. Also, in the list in the table of "Proposed Assays" I don't see any description of sequencing of the vector plasmids, or of the provirus in the vector producing cells or transduced cells. • The manufacturing section for the lentiviral vector is very brief -- who will be doing what lot release testing? How will the vector be produced and purified? There's a statement in the proposal from one contract manufacturer that says the vector plasmids will be "appropriate grade". The FDA will want that to be GMP-grade, but I don't see that indicated in the proposal. • I haven't found any mention of a quality infrastructure in the proposal, so it's hard to comment on the nature of the quality program. However, the contract manufacturer says they do manufacturing according to GMP, so that should provide quality infrastructure. • Since the expression of the modification to protect the mature T cells from HIV infection by preventing fusion is important, they should incorporate this into their product characterization scheme.
No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 13	• The project is feasible. The team is qualified and has all necessary resources to perform proposed work. • The project is ambitious, but feasible. • Yes, the development pathway as outlined does not raise any major concerns since it is a well-trod pathway. • This is a highly qualified team. The PI has extensive expertise using the mouse model to study HIV and has assembled the other members of the team to complement and augment their expertise. • The institution has extensive resources available, with relevant letters of enthusiastic support from the institution guaranteeing access to those resources. • Project has great resources at the cell facility within the applicant institution. • The risk mitigation strategy has identified potential pitfalls and has identified additional funding sources to account for those delays, although low likelihood.
No: 0	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**

Yes: 13	• Their analysis has taken these concerns into account, and their discussion of these issues make it clear that they are well aware of the problems of health care disparity in this population. They will attend conferences and seminars where such issues are discussed while also tapping into abundant resources at the applicant institution that manage health care of people living with HIV. • The project addresses a problem that disproportionately afflicts people of gender and ethnic/racial minorities, as well as the homeless and people who use drugs. • Successful development of this therapeutic strategy would highly impact California's diverse and underserved populations that are disproportionately impacted by HIV disease. • The project will track the sex, race/ethnicity of stem cell donors. • Team members will be regularly educated in DEI. • Not sure how this therapy would be accessible (reimbursable) for unhoused populations. • The team should consult with community members when designing the clinical trial.
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	• Great data and great institution with strong, demonstrated track record of DEI considerations related to clinical trials. • Successful development of this therapeutic strategy would highly impact California's diverse and underserved populations that are disproportionately impacted by HIV.
6-8: Responsive	1	*none*
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-14716
Title (as written by the applicant)	Targeting multiple myeloma (MM) with BCMA CAR NK cells expressing a targeted bispecific antibody
Translational Candidate (as written by the applicant)	BCMA CAR NK cells derived from CD34(+) umbilical cord blood hematopoietic stem cells
Area of Impact (as written by the applicant)	Patients with multiple myeloma (MM)
Mechanism of Action (as written by the applicant)	Bispecific antibody BCMA CAR NK cells are umbilical cord blood-derived CD34+ hematopoietic stem cells that are engineered to produce two agents - BCMA-CAR NK cells and a bispecific antibody - thus targeting BCMA and two other antigens expressed on the surface of MM cells and eradicate MM cells effectively.
Unmet Medical Need (as written by the applicant)	Although BCMA CAR T cells have been approved by the FDA, MM is still an incurable disease. BCMA CAR T cells show good response, but most patients eventually relapse. Patients treated with BCMA CAR T cells experience cytokine release syndrome (CRS) and neurotoxicity.
Project Objective (as written by the applicant)	Complete Pre-IND submission and finalize IND plans
Major Proposed Activities (as written by the applicant)	• Manufacture bispecific antibody (BsAb) BCMA CAR NK cells • Conduct PK/PD studies • Pharmacology and toxicity studies • Optimize treatment schedule of BsAb BCMA CAR NK cells in efficacy testing • Confirm efficacy of BsAb BCMA CAR NK cells under optimized and safe conditions • Pre-IND submission
Statement of Benefit to California (as written by the applicant)	In the United States, the lifetime risk of getting multiple myeloma is 1 in 132 (0.76%). For 2022 in the United States alone, the American Cancer Society's estimates about 34,470 new cases of multiple myeloma will be diagnosed. Blacks may be twice as likely as whites to develop multiple myeloma. 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	$6,036,001
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	2
Highest	95
Lowest	88
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/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	• Although there are two approved CAR T therapies for multiple myeloma (MM), and several other biologic drugs, there remains a need for potentially curative therapies that are more accessible and affordable, and can address tumor relapse. The proposed product addresses these issues and is likely to have major impact in the treatment of multiple myeloma patients. • This proposal addresses the unmet need for an immediately available, off-the-shelf CAR NK / bispecific Ab (BsAb) product to treat MM. The product eliminates the need for autologous manufacture, which is costly, lengthy and limits access. • The novel construct design in this proposal offers a value proposition in the "off the shelf" allogeneic approach and the potential for a safer and more effective therapy. • This is an off-the-shelf product for an unmet medical need.
No: 0	*none*
GWG Votes	**Is the rationale sound?**

Yes: 14	• Yes. These bispecific Ab (BsAb) secreting BCMA CAR NK cells may be superior to prior approaches, with better efficacy and safety.
	• Overall the preliminary data support the rationale. There are a few outstanding questions that should be addressed in future studies.
	  ◦ It is unclear what the half life is of the secreted bispecific antibody (BsAb) is. The authors state that they have previously manufactured a different BsAb that had a short half-life (less than one hour in vivo). They claim they have overcome this issue by incorporating IgG4 Fc into the proposed BsAb. However, they don't provide data comparing the new IgG4 Fc fusion BsAb to the original design, nor do they provide half life data for the proposed BsAb.
	  ◦ The applicant does not provide data characterizing the potential immunogenicity of the BsAb. Does this BsAb trigger antibodies? Can it be repeatedly administered in patients? Or will it be rejected?
	  ◦ A final data gap relates to the ability to re-dose and re-administer the CAR NK product. An attractive feature of CAR NK cells is their potential to be re-administered, but the applicants don't provide data supporting this possibility.
	• I appreciate that the authors sought to mitigate the short half life of the secreted BsAb by linking it to the IgG4 Fc. However, half life data for the IgG4 Fc-linked product are not provided. However, I also recognize that data from vitro or in vivo mouse studies are unlikely to be predictive of the proposed product's half life in humans.
	• The rationale is sound based on published and preliminary data.
	• This is an experienced team with strong preliminary data.

No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 14	• Yes, overall the project is well planned. The proposed milestones are intended to address some of the outstanding data gaps in the application. • Yes. The project plan is detailed, rigorous and likely to translate to the clinic, as a similar (non-competitor) NK product is currently being tested in a phase I clinical trial. • Overall, yes, though there are a few gaps in the description of analytics development.
No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 14	• This is a top notch applicant with deep history in the development of NK cell therapies for cancer. They have a great track record and access to the necessary support staff and team. • The team has experienced staff. Any potential hurdles will be analyzed and resolved in a timely manner.

	• I have no concerns. The team is well-poised to conduct the project, plans are well laid out, and decision points are very clear. • Future trial plans are also clear, with appropriate safety criteria. • The applicant has a clear understanding of the regulatory process.
No: 0	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 14	• The applicant clearly describes the disproportionate impact of MM on African American populations. They also go beyond disease burden and discuss the need for diverse community representation in the healthcare workforce, especially among clinical trial staff. • The applicant discusses the possibility of safely delivering their therapy in local community clinics, nursing or residential homes, and other outpatient settings for the benefit of medically underserved groups. • The applicant's plan outlines DEI principles for clinical trial participants and staff. • DEI values are reflected in the applicant's approach.
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: 7.0

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	• The applicant's goal is to develop an off-the-shelf cell therapy that is appropriate and accessible for any patient regardless of race, ethnicity, age or socioeconomic status. • The applicant talks about the cost of developing the product being less than current options, thus making it accessible to more uninsured and underinsured patients. • The applicant team seems to embrace the need to provide a treatment that is accessible to underserved populations. • Proposed studies use a diverse population of cells from three sources of umbilical cord blood (UCB) donated from mothers of both male and female babies of various racial and ethnic backgrounds, including white and Black, Asian, and Hispanic donors. • The applicant will source donor cells from a diverse cohort. • The number of underrepresented minority (URM) patients that seek out care at academic medical centers, like the applicant institution, is disproportionally lower than the population in the center's catchment area. This applicant institution has aggressively worked to reverse this trend. • The institution is strong with regard to to DEI for clinical trials. • The application is responsive to DEI values.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-14613
Title (as written by the applicant)	Novel T cell immunotherapy for lung cancer
Translational Candidate (as written by the applicant)	Restricted, antigen-specific T cell receptor (TCR)-engineered T cells
Area of Impact (as written by the applicant)	Metastatic lung cancer patients who fail to respond to immune checkpoint therapy or prior treatment
Mechanism of Action (as written by the applicant)	Despite the impressive clinical response to immune checkpoint inhibitors, the majority of lung cancer patients fail to respond to the immune checkpoint therapy, and this remains unmet medical need. The proposed candidate comprises T cell receptor (TCR)-engineered T cells that can recognize and eliminate CT83 antigen-expressing lung cancer cells, leaving normal cells untouched. This is because CT83 is highly expressed in lung cancer cells, but not in normal cells.
Unmet Medical Need (as written by the applicant)	Despite the impressive clinical response to immune checkpoint inhibitors, the overall objective response rate in lung cancer patients is approximately 20%. Therefore, the majority of lung cancer patients fail to respond to the immune checkpoint therapy, and this remains unmet medical need.
Project Objective (as written by the applicant)	Pre-IND meeting with FDA; readiness for preparing an IND
Major Proposed Activities (as written by the applicant)	• Generate GMP-compliant Master and Working Cell Banks, viral particle production, and certificate testing required by FDA • Non-clinical studies (biodistribution/fate of T cells, pilot toxicity), GMP-compatible scale up process of TCR-T cell product, stability tests • Regulatory and clinical trial development (IRB protocol) and Pre-IND meeting with the FDA
Statement of Benefit to California (as written by the applicant)	Lung cancer is a leading cause of cancer-related deaths in California and in the county where our institution resides, which is racially and ethnically diverse. There are alarming racial/ethnic disparities in lung cancer outcomes in our county. HLA-A*02 is expressed in 40-50% of the general population. CT83 is highly expressed in approximately 50-70% of human non-small cell lung cancers (NSCLCs). Thus, the proposed research will benefit the state of California and our county.
Funds Requested	$5,689,540
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	89
Median	90
Standard Deviation	3
Highest	90
Lowest	80
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	12
(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: 12	• Since only 20% of lung cancers respond to the current most effective treatment, there is a need for new approaches. This product could be therapeutic for a portion of refractory lung cancer patients. • The unmet medical need is poor survival and the inefficiency of current therapies for advanced stages of lung cancer. Only 20% of lung cancer patients will respond to checkpoint inhibitor therapy. A large proportion of refractory patients have no good therapeutic options. • The modified T cells in this proposal target a newly identified tumor antigen, called CT83. This antigen is expressed in 50-70% of human lung cancers, including non-small cell lung cancer (NSCLC, the proposed target indication). The modified T cells will only target cells that express HLA-A2, which is present in 40-50% of humans. The applicant has not identified more specifically how those two groups intersect (i.e., the prevalence of tumors expressing CT83 in patients that express HLA-A2), but a minimum of 25% of lung cancer patients could be eligible for this therapy (maybe more). • The technology boosts the expansion of T-stem cell memory. If development is successful, this could significantly improve patient care. • The project will have a strong impact on lung cancer patients.
No: 1	• Although NSCLC remains a popular target for therapeutic development, the proposal does not make an adequate argument for recruiting patients in a highly competitive field.
GWG Votes	**Is the rationale sound?**

Yes: 13	• Yes, generally. This immunotherapy project is based on combining three novel features into the genetically modified T cells, in addition to the CT83-targeted T cell receptor, to improve success:
	  ◦ 1) Incorporation of a novel signaling domain that enhances anti-tumor immune responses. The data in Figures 7-10 show support for this claim.
	  ◦ 2) Replacing the human TCR constant region with the murine counterpart. The purpose of this modification is to decrease pairing with endogenous human TCR beta or alpha chains.
	  ◦ 3) Incorporation of an additional therapeutic shRNA into the expression construct that goes into the T cells. Figure 11 provides data to support this claim in a mouse model.
	• There are two major innovative advantages (i) selectivity of the target (HLA-2 restricted CT83) and (ii) a novel signaling domain, which increases the potency of the proposed product.
	• The concern from the prior review was about the potential immunogenicity of murine TCR constant regions and lower cytokine secretion by CAR-modified T-cells. The applicants responded to all questions, providing a sufficient explanation.
	• The rationale is supported by the data presented in the application.
	• Very sound rationale has been provided.
	• The rationale is adequately explained.
	• The scientific rationale is sound.
	• Overall, yes, although data on tumor heterogeneity would also be important.

No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 12	• Generally the project plan has been developed in a well-considered way. • Yes. The project is well planned and supported with excellent preliminary data. • The project is well planned. The proposed studies will be sufficient for process validation in the GMP environment and conducting engineering runs as a requirement for CMC. • Overall, yes, but the monitoring proposed for the clinical study is too vague. Patients will be followed by testing at three, six, and twelve months after treatment, and yearly for up to fifteen years. What testing will be performed?

	• Overall, yes, though there are some concerns about dosing, based on preclinical evidence.
No: 1	• From the proposal, it is difficult to ascertain the applicant's ability to produce the proposed product.
GWG Votes	**Is the project feasible?**
Yes: 13	• Yes. For vector manufacturing, the applicant will partner with an organization with a long track record of GMP manufacturing and testing of lentiviral vectors. They will be using a recently opened GMP facility at their institution for cell processing. • The concept is feasible. The early development of a qualified, in vitro, potency assay would be helpful for successful CMC controls. The proposal states that the cytokine release does not correlate with the cytotoxicity assay. This observation should engender additional characterization of multiple drug product lots. • The timeline of proposed milestones is appropriate. • The team is qualified to perform the proposed studies. • The team has access to all necessary resources to perform proposed studies. • The contingency plan and risk mitigation are described in the application.
No: 0	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13	• Yes, they have developed and provide good data to indicate that the plan accounts for DEI issues. • The DEI plan appears adequate at this stage.
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	• The applicant outlines the potential benefit of the proposed product on health equity, noting that it could benefit a broad and diverse lung cancer patient population. • The project plan includes age-matched male and female mice to investigate the potency, biodistribution and toxicity of the product. • The team will work with the institution's cancer center to develop DEI strategies, including training of cancer care providers, researchers, and staff. They plan to conduct engagement via the institution's office of community engagement, and access "wellness hubs" - are community-based programs through which investigators disseminate findings from cancer research to community residents. • Plans include DEI training for the clinical team. • The application reflects DEI values. • The study has an inclusive design.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-14623
Title (as written by the applicant)	Telomerase mRNA for short telomere related pulmonary fibrosis
Translational Candidate (as written by the applicant)	Nucleoside-modified mRNA encoding telomerase reverse transcriptase (TERT) encapsulated in a lung-targeting lipid nanoparticle (LNP) delivered intravenously.
Area of Impact (as written by the applicant)	1) Idiopathic pulmonary fibrosis (IPF) and 2) other diseases and conditions caused or exacerbated by short telomeres.
Mechanism of Action (as written by the applicant)	Telomerase reverse transcriptase (TERT) mRNA lipid nanoparticles (LNPs) transiently extend the telomeres of alveolar epithelial cells of the lung, enabling cell division that repairs lung structure and function, delays cellular senescence, and limits chronic secretion by the senescent cells of inflammatory pro-fibrotic molecules. The extension of the telomeres occurs over a few hours, after which the extended telomeres resume shortening at their normal rate. This telomere extension reverses years of telomere shortening.
Unmet Medical Need (as written by the applicant)	Idiopathic pulmonary fibrosis (IPF) is a fatal disease brought on by shortened telomeres that results in death by gradual suffocation, with median survival of only 3–5 years following diagnosis. Our one-shot treatment delivers a therapy that extends telomeres by transiently boosting telomerase activity.
Project Objective (as written by the applicant)	The performance of IND-enabling studies.
Major Proposed Activities (as written by the applicant)	• Pharmacokinetics (PK) and dose determination of i.v.-injected TERT mRNA LNPs. • Pharmacodynamics (PD), biomarker, and comparative studies to FDA approved idiopathic pulmonary fibrosis (IPF) drugs and pharmacology in IPF patient cells. • CMC activities (scale-up, assay methods and stability) for manufacturing of TERT mRNA LNP production.
Statement of Benefit to California (as written by the applicant)	Idiopathic pulmonary fibrosis (IPF) is a serious illness with no cure for which there is a high unmet medical need for treatment. In the US, the vast majority of patients with reported IPF are non-Hispanic whites yet Hispanic populations have earlier onset and worse outcomes of the disease, as do minority patients in general. The relatively high numbers of Hispanic citizens in California make this disease one of particular interest to the medical community in the State.
Funds Requested	$3,984,942
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	89
Median	90
Standard Deviation	2
Highest	92
Lowest	86
Count	11

(85-100): Exceptional merit and warrants funding, if funds are available	11
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/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: 11	• Idiopathic pulmonary fibrosis (IPF) is a heterogeneous disease that has poor long term prognosis; the standard of care is symptom amelioration relief only. A therapeutic option that intervenes in disease progression is sorely needed.
	• Overall, this proposed product offers a sufficient, impactful and practical value proposition for patients and health-care providers. In support of this statement
	  ◦ The proposal outlines cost estimates of the effectiveness of this proposed product. The applicant's data, taken at face value, indicates this product could offer a more valuable treatment option than currently available therapies.
	  ◦ To patients, this therapy could offer a long-lasting, disease-altering and relatively unobtrusive therapeutic. It is likely that a single (or potentially a few) treatment rounds would be sufficient, as opposed to chronic treatment with the drugs available today. Taken together, these would appear to offer a strong value proposition to patients.
	  ◦ For health care providers, this therapy would offer a promising treatment modality in an area of great unmet need. Furthermore, since this would be given in short courses of treatment, rather than repeatedly, it could would have a limited burden on the health care system.
	  ◦ Finally, if this therapy can reduce the need for IPF patients to progress to lung transplant, that would free up available organs for other patients and also reduce the high cost and care burden of organ transplantation for IPF patients.
	• Yes, IPF has a clear unmet need and there is supportive evidence that telomere shortening plays a role in the disease.
	• This is a strong proposal and has the potential to impact IPF, which is a disease with a poor prognosis and a median survival of about 5 years.
	• There are relatively few treatment options available for IPF. Two recently approved medications (pirfenidone and nintedanib) offer improvements in quality of life and symptoms such as shortness of breath, but not disease-altering treatments that affect the overall outcome. IPF remains a fatal diagnosis.
	• The proposed therapy is not a stem cell technology, per se. It would increase telomere length in targeted cells in the lung. The effect of the proposed product would be to increase telomere length, thereby decreasing rates of cellular senescence. This, in turn, would impact disease outcomes. This is shown by their current preclinical data in an animal model.
	• Despite not being a stem cell therapy, per se, this is a novel therapeutic approach that offers potential to impact outcomes in a serious, fatal disease.

No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 11	• The applicant has addressed GWG concerns from the previous submission appropriately. • The addition of data showing telomere extension in mouse models and in human epithelial cells is supportive. The efficacy data in the bleomycin-treated short telomere mice is helpful but on the edge of significance for lung function, and has a low and non-standardized number of mouse replicates. • This is a well-constructed and sound proposal. The rationale is justified given that many patients with IPF have short telomeres, which is the primary focus of this treatment (Fig 2). The therapy would target specifically the AT2 cells in the lung, which have recently been identified as important in the pathogenesis of IPF, with numbers of AT2 cells reduced in these patients and remaining cells demonstrating a senescent phenotype.

	• The applicant provides a good set of supporting data to justify the rationale and potential of this therapy in IPF. • The applicant shows the efficacy potential of the product in several studies. Using the bleomycin model, they show improvements in survival (Fig 17), lung function (Fig 18), lung fibrosis (Fig 19), and lung architecture (Fig 20). • The applicant discusses how this therapy would extend telomeres only transiently – an important point given the link between continuous expression of telomerase and cancer formation. • The applicant acknowledges the need to supplement their existing data with an additional animal model, measurement of collagen in treated animals, and degree of fibrosis.. The other major need in terms of the preclinical studies is to test TERT-101 in the setting of background therapy (pirfenidone and/or nintedanib). These studies are all planned as part of the grant. • The applicant has conducted initial toxicity studies that did not yield any concerning findings (Fig 5-6), as well as characterization data and initial stability data (Fig 4). However, the stability data to date is only up to 1 week, which is very short. • Overall, as outlined above, I feel that the preliminary data provided, coupled with the well-described plan, support development of this product. • Regarding the proposed toxicology studies, the applicant should note that it is important to ensure the dosing regimen (e.g. route of delivery) mimics the planned clinical dosing. • Yes; the rationale is adequately explained in this proposal.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 11	• The investigator has addressed concerns appropriately from previous submission. • The proposal includes responding to concerns raised by the FDA in their INTERACT meeting and preparing the group for a successful Pre-IND meeting. • The CMC development is well designed and appears reasonable. • The authors have outlined several quality considerations that will support their efforts. These include hiring a QA consultant and implementing a quality management system (QMS), which is briefly described at the top of page 27. These efforts appear sufficient and appropriate for this stage of product development. • I believe that the proposed timeline is certainly feasible, although it seems rather generous (long). For most of the items on the timeline (page 30), the time allocated seems generous and I would encourage the applicant to attempt to expedite their work. As some potential examples, please consider the following items: ◦ The applicant allocates between 2 and 4 quarters for "mouse and drug product preparation". This reviewer is not familiar with the specifics of the mouse preparation, but it seems very generous that it could take up to a year to prepare the mice and drug product for a preclinical study. • The applicant allocates a full 2 years to obtain patient samples and perform in vitro pharmacology studies. This appears long given that they state that they plan to study cells from 6 IPF patients. • The allocation of time for method transfer to the CMOs and engineering batch production generally appear long. One quote states a duration of 10-14 months from tech transfer to release of a GMP batch, while the timeline of the applicant appears to allocate ~18 months to this effort. • The silica studies are not scheduled to start until quarter 3 of the proposal, although the need for data in a second animal model may be a key limiting factor. The applicant should consider beginning this work earlier, if feasible.
No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 11	• A concern is the time and success associated with tech transfer and CDMO work. Experience indicates that there should be a level of caution associated with timelines. Often there is need for extension of timelines due to delays. • Yes; the proposed milestones and key project outcome (a successful pre-IND meeting) are likely to be achieved within the proposed timeline. It may be possible to accelerate this timeline. • The authors describe their team in depth, and all indications are that the team is well qualified, well staffed, and well positioned to perform the needed work.

	• The team appears to have access to all necessary resources, including preclinical resources (materials, labs, animal strains), tech transfer and CMOs, and consultants to assist with quality issues and regulatory filings. • The proposal also includes a number of letters of support, which is good to see. • The team outlines a number of risks in their proposal (p 27 and 34-35). These plans seem thorough. • The two major preclinical risks seem to be issues with demonstrating an effect in the silica model (or challenges in establishing the model), and if sufficient benefit is not seen in the repeat bleomycin study regarding OH-Pro deposition or fibrosis in the lungs of those animals.
No: 0	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 11	• The proposal outlines a sufficient DEI plan. • The applicant discusses their approach regarding diversity, equity and inclusion in a thorough manner in the proposal. Their approach appears strong, well-considered, and without gaps. • The applicant identifies their plan to conduct the proposed clinical trials at clinical centers throughout California, including under-represented groups. Their specific plans here are only discussed at a high level, which is fine because clinical trial design comes later in product development. • The authors also identify that IPF may occur more frequently in patients with socioeconomic vulnerability, including veterans, and state their intent to incorporate these considerations into their clinical trial design. • The authors describe, at a high level, their plan to prioritize participates from the most vulnerable communities in California. Details as to how this will be achieved are unclear.
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	1	• Applicant states it is unclear if the disparity in disease burden has a genetic basis or is due to selection bias in reported studies, but what is clear is that in general, minority patients with pulmonary diseases such as IPF have worse outcomes than non-minority patients. • It appears that socioeconomic status and exposure to environmental pollution may contribute to poor outcomes for disadvantaged or underserved communities. The applicant includes an interesting discussion in the application of CES score and disease prevalence. • The applicant states they believe that treatment should be equally accessible and affordable to all individuals with IPF. The development of a therapeutic that requires only a few doses for the treatment of IPF could help level the playing field for disadvantaged patients. • The applicant is involved with two patient organizations that are assisting them in outreach to patients with diverse backgrounds to gains insights into their perspectives. • The applicant states they will conduct the future trial(s) using selection of populations, biomarkers, and outcome measures

		such that differential characteristics of the treatment within any subgroup become evident. ● The applicant states that they have begun to design plans to follow best practices in recruiting and management of the clinical trials, including ensuring that under-represented groups are included. ● The applicant states that all employees will take training in cultural sensitivity and DEI. ● The applicant plans to construct sex-balanced preclinical and clinical study populations. ● The applicant has implemented a policy that all consulting partners and large corporate partners must confirm that they have implemented DEI policies.
6-8: Responsive	3	● The application includes a good demographic analysis.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-14062
Title (as written by the applicant)	Escape-Resistant Oligonucleotide Therapy (ONT) for Cytomegalovirus (CMV) Disease in Hematopoietic Stem-Cell and Solid-Organ Transplant Patients
Translational Candidate (as written by the applicant)	Cytomegalovirus (CMV) antiviral DNA oligonucleotide therapy
Area of Impact (as written by the applicant)	Hematopoietic stem cell transplant (HSCT) recipients can experience rejection and childhood cognitive and hearing impairment caused by cytomegalovirus (CMV)
Mechanism of Action (as written by the applicant)	The candidate oligonucleotide therapy (ONT) disrupts viral IE feedback circuitry and breaks homeostatic control of cytotoxic proteins inducing apoptosis in infected cells.
Unmet Medical Need (as written by the applicant)	Treatment-resistant CMV is the leading cause of transplant rejection and childhood deafness and cognitive impairment. Current standard of care countermeasures (e.g. ganciclovir) are subject to escape and excessive toxicity. The proposed therapeutic is robust to escape and exhibits a favorable toxicity profile.
Project Objective (as written by the applicant)	Pre-IND submission
Major Proposed Activities (as written by the applicant)	• Formulation • Animal Studies • Process Development and Scale-Up
Statement of Benefit to California (as written by the applicant)	California is ~40% Hispanic or Latinx, a population known to be at significantly increased risk of cytomegalovirus (CMV) infection and disease. CMV disease is a leading cause of transplant rejection and cognitive impairment in the US. An escape-resistant ONT-based intervention for CMV disease could have many advantages for California's diverse population over the current standard of care.
Funds Requested	$3,977,180
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: 88

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

Mean	88
Median	88
Standard Deviation	2
Highest	90
Lowest	85
Count	11
(85-100): Exceptional merit and warrants funding, if funds are available	11
(1-84): Not recommended for funding	0

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: 11	• Cytomegalovirus (CMV) infection has the potential to cause life-threatening disease in immunocompromised patients, including solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT) recipients. • CMV is also a leading cause of birth defects including deafness and cognitive impairment in newborns and infants. There is no effective vaccine for CMV. • Current antivirals, such as Ganciclovir, are effective, but have considerable dose-limiting toxicity and causing severe adverse side effects. The proposed project aims to address some of these limitations and to develop a brand new class of antiviral therapy, which is an oligonucleotide based drug product that is focused on feedback disruption in virally infected cells. • CMV remains a disease of concern, but one in which treatment options are limited. The proposed product has the potential to provide an option, and potential improvement, to the current standard of care. • CMV infection in immunocompromised patients post HSCT is a major issue in the field. Current CMV treatments have limitations. The proposed product, if incorporated into standard of care for transplant patients, will increase the adoption of stem cell transplants and improve patient care. • Viral resistance is a major concern and a major limitation for effective antiviral therapy. The proposed product is being developed with consideration to limit viral resistance and thus expand the patient population and clinical situations (such as organ transplant) for effective therapy. • CMV is a pathogen of major concern and drug resistance is a significant challenge. Both are well documented in the literature. • The proposed product offers a sufficient, impactful, and practical value proposition for patients and/or health care providers. • The applicant has an exceptional approach to provide impact. • The product appears to be designated for intravenous administration, a route that imparts significant cost and disruption for patients. Consideration should be given to routes that provide greater flexibility for patients and self-administration.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 11	• The overall rationale is sound and is based on the natural history of CMV. From a biological networks perspective, protein inhibitors (the current standard of care) target individual nodes, allowing easy escape by single point mutations. • The applicants propose to use an oligonucleotide-based approach to target a node that is part of an essential negative feedback loop, practically eliminating the chance of CMV resistance. • Yes, the preliminary studies are beautifully designed and executed and contain the relevant controls in support of the product. • The overall data support the proposed rationale and mechanism of action for the drug product being developed. • This strategy rests on the groups extensive history of studies characterizing CMV gene-regulatory circuitry and is based on an initial report published in 2022. The strategy was also shown to work for other herpesviruses and is being developed, in parallel, for HSV1 and HSV2. • A particular strength of the proposal is the use of a murine version of their product that is tested in mice (aged or immunodeficient) infected with CMV. It would be good to compare resistance to Ganciclovir in vitro as in Fig. 12 which compares the proposed product to Fomivirsen (DNA antisense, which is no longer in use). • The scientific robustness of the program is exceptional. The researchers have a deep understanding of the virus and have thoroughly investigated a novel approach to regulate viral replication and disease. • The clinical/real world application of the drug product has not been as well investigated and the challenges of transitioning from research to development may be substantial. Areas for improvement include 1) clarification on the experience the manufacturing site has with overall CMC for the GMP production of an oligonucleotide; and 2) greater

	consideration of safety assessment for an oligonucleotide product intended for commercial use and for a diverse patient population.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**

Yes: 10	• The project is appropriately planned, and designed to achieve meaningful outcomes.
	• This is well-constructed, quality program.
	• Yes, the overall plan and timeline are both feasible and demonstrate an urgency in line with CIRM's mission.
	• Overall, yes, with a few comments.
	  ◦ The in vivo experiments presented appear to be preventative models or lack sufficient detail to determine the schedule of events to determine if any treatment models have been tested. It is also not clear if treatment models are planned (i.e., no pre-infection dosing).
	  ◦ Safety studies include body weights and RNAseq analysis of organs. There seems to be no mention of other basic studies such as cbc, chemistries (e.g. LFTs), cytokine panel, necropsy. Further, how will terminal RNAseq data be used to interpret toxicity (which could have peaked much earlier and subsided from the standpoint of RNA signatures)?
	• The program is generally well constructed and has a focus on quality, i.e., identification of key challenges and means to address the challenges.
	• The team has a reasonable plan, but one that also appears to be reliant on a previous program for a phase 0 clinical trial for oncology. It is not clear the previous experience is of sufficient depth and breadth to address the challenges of an oligo product, a unique construct, and intervention for a viral-based disease.

No: 1	• In vivo studies from the preclinical work may lack details on the model being more representative of treatment.
GWG Votes	**Is the project feasible?**
Yes: 11	• The overall project and milestones are feasible and have a high probability of being successful within the proposed timeframe of the program. • The product plan and timelines are appropriately aggressive for the clinical need, while being appropriately conservative for consideration of patient needs and safety. • The proposed team is highly qualified (and staffed) to address the challenges of an anti-viral product and patient needs and challenges. • The team could be further expanded to include individuals that are experienced in nonclinical development. • The proposed team is appropriately qualified and staffed. • This is a well qualified team. • The team has access to all the necessary resources to conduct the proposed activities. • Well thought-out plans are presented for each of the four risks identified. • Overall contingency plans are thoughtful and appropriately manage the associated risk. The only major issue relates to the potential for the FDA to require a second animal study. The applicants expect this to be a second mouse study, but the agency may require a non-human primate study for this type of drug product. The applicant has not accounted for this possibility. • Overall, yes, but manufacturing capabilities around product disposition are not clearly established in the application. • The complexity of manufacturing a 56mer oligo should be considered.
No: 0	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 11	• DEI is well addressed both in the design of experiments (e.g. cells from diverse donors, use of male and female mice) and in community outreach efforts. • The applicants outline in vivo and in vitro studies to address the potential effects of age on the utility of their product, as well as studies in cells isolated from a diverse patient population. These efforts address diversity in a manner appropriate for this stage. Clinical trials will be required to determine if there are potential DEI-related limitations associated with the proposed product. • The outcomes would inform the development of a product or tool that serves the unmet medical needs of the diverse California population. • Yes; the applicant does a great job on the DEI front.

	• Overall, yes, though at this early stage the applicant may not have provided appropriate attention to DEI. They may have some confusion about CIRM funding of DEI-oriented activities.
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: 6.0

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	• While DEI-oriented patient activities are far off, it still seems that the DEI plan covers all the required points in a cursory manner. As an example: there is a typo in the budget detail describing the institutions doing the DEI activities. More to the point only $45,000 is budgeted. • The rationale for addressing CMV as a "neglected infection of poverty" is well taken, but a bit confusing. The narrative describes the very high incidence of the infection among Latino populations, but the map shows low infection rates in areas with high Latino populations (California, Arizona, and especially New Mexico) with highest rates primarily in the South. • The plans for community engagement were impressive including media outreach, advisory groups and the like, but there was little budget support for this activity. • The proposal includes good data analysis on demographics. The applicant undertook thoughtful determination around tissue selection related to broad sample characteristics. • Yes, but the proposal includes limited budget support for DEI related efforts. • Yes, but the proposal includes limited review of incidence and prevalence. • The applicant appears to embrace DEI values.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-14609
Title (as written by the applicant)	Enhanced Autologous Pancreatic Islet Transplantation and Survival for Diabetes Mellitus Therapy
Translational Candidate (as written by the applicant)	'Pseudoislets' derive from human islets, but compared to islets have superior survival, function, and diabetes reversal after transplantation.
Area of Impact (as written by the applicant)	Pseudoislets could transform islet replacement strategies in diabetes by increasing the number and durable function of transplanted islet cells.
Mechanism of Action (as written by the applicant)	Transplantation of replacement human islet cells is approved in type 1 diabetes and chronic pancreatitis. Sadly, this approach is limited by the scarcity of donor islets, and poor islet survival after transplantation. Pseudoislets - clusters of islet cells derived from human islets - could address this need. Compared to islets, pseudoislets are smaller, resilient, and interactive after transplantation with blood vessel cells, leading to improved islet cell survival and lasting function.
Unmet Medical Need (as written by the applicant)	Loss of islet transplant function in subjects electing total pancreatecomy and islet autotransplantation (TPIAT) is an unmet medical need. Autologous pseudoislet transplantation could prolong islet graft survival and function in TPIAT subjects, extending insulin independence and euglycemia.
Project Objective (as written by the applicant)	PreIND meeting on auto-pseudoislet transplantation
Major Proposed Activities (as written by the applicant)	• Develop manufacturing and regulatory processes to generate GMP human pseudoislets for autotransplantation in subjects at risk for diabetes mellitus. • Assess the stability, function, and the capacity for diabetes reversal by GMP human pseudoislets in transplantation studies of diabetic mice. • File a pre-IND for human pseudoislet transplantation to the U.S. FDA
Statement of Benefit to California (as written by the applicant)	Multiple benefits to California and its citizens would ensue from successful conclusion of the innovative studies proposed here. This includes (1) improvements in patient care, especially for those requiring islet transplantation, (2) emergence of pancreatic islet autotransplantation programs that would foster increased consultation and use of California health care systems by citizens and outside clients, (3) enhanced support for academic training and research in pancreatic islet transplantation.
Funds Requested	$6,056,713
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: 88

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

Mean	86
Median	88
Standard Deviation	6
Highest	95
Lowest	70
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	11
(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: 12	• Long-term control of glucose remains an unmet medical need for individuals with impaired islet function. This is a major burden not only on the individual but for public health budgets in the US as well as around the world. • If pseudoislets can significantly increase the number of individuals who maintain normal glycemic control for many years after TPIAT, then the proposed product clearly offers an impactful, practical value proposition for patients who must undergo that surgical procedure. • While TPIAT is a relatively uncommon procedure, the affected population has an acute medical need that currently is only partially addressed by autotransplantation, which fails immediately or over time for the large majority of patients. • The development of this product would certainly advance knowledge in the field, and would improve the standard of care for patients if successful. • The potential for successful islet replacement offers significant advantages over current standard of care treatments for these patient populations. • This product would be impactful for intended disease. Although this is a limited patient population, if the product is successful it could be generalizable to indications with larger patient populations such as Type 1 Diabetes (T1D). • This product has the potential for treatment of T1D overall, not just post-pancreatectomy. • If successful, this drug product would have a substantial impact for patients with chronic pancreatitis and potentially those with diabetes. • Extending the technology to help treat other forms of diabetes, especially type 1, via cell therapy would dramatically strengthen the long-term value proposition. • This product may impact a broader group beyond the current selected disease indication, but this small patient population may challenge clinical development.
No: 1	• Their goal of improving total pancreatectomy with islet auto transplantation (TPIAT) is to increase the duration of insulin independence. If that was achieved, it would provide patient benefit over the long term. • The applicants are targeting a treatment for a subset of patients diagnosed with chronic pancreatitis with refractory abdominal pain. They do not provide any detail on the incidence or prevalence of this subset. A publication by Lara et al (Pancreas, 2019) reports that in the US there were 825 TPIAT between 2002 and 2013 for chronic pancreatitis. This is an exceedingly small population to attempt a clinical development program. • The applicants state that alcohol and tobacco use are prominent in patients with the disease. The ability to successfully deliver a cell therapy to these patients will require significant support and behavior modifications. Patient eligibility requirements at this point are not clear. • Clinical trials for this indication would be difficult to enroll and conduct successfully. • The specific product proposed here is unclear. Are the applicants proposing an improved procedure for autologous cell processing? What would be the commercial interest to provide funding for later stage (i.e. larger) clinical trials? • Studies in an immunocompetent diabetic mouse model may be needed to demonstrate the efficacy of this product. • The persistence of the transplanted cells is unknown and will affect the durability of the product.
GWG Votes	**Is the rationale sound?**
Yes: 12	• The applicants provide evidence that pseudoislets are more potent than "standard islets" in insulin production and remain active for a longer time after transplantation in mouse compared to "standard" islets, possibly because they display a relatively immature initial phenotype and express factors that promote vascularization. • The process developed by the investigators generates "pseudoislets" that are biologically similar to "natural" islets but have superior properties for transplantation into patients. Use of the pseudoislets seems likely to improve outcomes of autologous islet transplantation with minimal risks of extra complications. It is likely that the approach

	could be extended to allogeneic transplantation from natural islets and possibly to islets generated from adult or pluripotent stem cells. • The development of GMP pseudoislets is based on preliminary data that suggests the successful ability to produce this drug product for the studies proposed. • The data generated to date support the further development of this cellular drug product. • The rationale is straightforward and sound, even if the mechanistic basis is only incompletely understood. • In vivo data are limited but encouraging. The issue of persistence of human cells is difficult to address in mouse models. • In vivo data modestly support the proposed mechanism of action. • The rationale is sound, however the persistence of the effect should be addressed to demonstrate how this product relates to standard of care. • The data provided do not support further development, but overall concerns are driven by the choice of the indication, patient population, and available standard of care. • The applicants present data suggesting effects related to mechanism of action. The only figure that shows in vivo data that goes to efficacy is Figure 5, and the effect is modest. • The applicants suggest that removing extracellular matrix during pseudoislet manufacturing enhances islet function and survival by improving diffusion and reducing hypoxia. This is somewhat counter to the argument that cells are more productive in their native microenvironment.
No: 1	• Studies in a more translatable, immune competent animal model are needed to support further development.
GWG Votes	**Is the project well planned and designed?**

Yes:
12
	• The milestones and activities are laid out systematically to transition from a research laboratory based-procedure to a GMP process. The process will initially be developed using donated cadaveric islets. Once it has been appropriately advanced and derisked, it will be carried out on islets from living donors. Because only a small fraction (10%) of living donors islets will be processed in the initial studies, the risk of compromising a medically necessary procedure appears small.
	• The timeline and project plan are conservative and responsible, in the sense of developing methods initially using cadaveric human islets before proceeding to living donors. The timeline to reach the milestone of a pre-IND is still tight enough to demonstrate the commensurate urgency.
	• The proposed studies are well designed to support manufacturing of this novel cell product.
	• The applicants present a practical and achievable project plan.
	• This program is well designed from a quality perspective, and relies heavily on the GMP CDMO experience to guide the program forward.
	• This project is appropriately designed for the successful development of a GMP compliant drug manufacturing process. There are minor issues with the QC lot release program, but these can be overcome with minor changes to the testing plan.
	  ◦ Specifically, the release testing program is missing tests for total cell count and cell identity.
	  ◦ It is also highly recommended to test for both insulin and glucagon throughout development and as part of lot release.

No: 1	• The applicants should emphasize studies that will provide early signals of durability, as these data will be important to maintain an interest in further funding for clinical trials. • Much of the application is for manufacturing activities, but stronger potential for efficacy and proof of concept data are needed. The applicants plan to use a diabetic mouse model to detect differences between control islets and pseudoislets. They should consider statistical design of the studies to be able to determine the effect size, which may not be large. • Further proof of concept work is needed before a large investment in CMC is worthwhile.
GWG Votes	**Is the project feasible?**
Yes: 12	• The milestones and activities are laid out clearly, and it appears that the team should be ready for presentation of a novel cellular product to the FDA in a pre-IND meeting within the span of the project. • The team is highly experienced in working with human islets. There are complementary skills in a lab "working group" and a strong academic center for the development of human cell and gene therapies. Members of the team have collaborated successfully for some years.

	• The resources of the research labs and the institution facility for GMP manufacture of cell and gene therapies appear outstanding. • The project may be feasible, but the competitive standard of care landscape should be taken into account. • The minimum time for duration of effect should be confirmed with patient advocates. A reasonable assumption for minimum duration is 1 year. • The timelines are reasonable and achievable from a CMC perspective. • The applicants present a good CMC plan. • One additional team member may be needed to support the external work with the CDMO. A significant amount of project management and data analyses will be required by the sponsor. • The future commercial viability of the product is unknown. • Clinical studies may be difficult to enroll due to the limited patient population.
No: 1	• The timelines are feasible. However, I don't know if the project is feasible because the future commercial viability of the product is not clear. • They have strong scientific expertise and experience, however I believe practical regulatory and clinical experience is lacking. This could be addressed.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 11	• The DEI plan is not project-specific, but the institution has a good track record in DEI. • The application addresses DEI efforts in a perfunctory manner.
No: 2	• Activities to account for DEI are not well explained. • DEI material seem to be cut-and-paste from a boilerplate template without specific inputs or details to this project.

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

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	• The applicants are at an outstanding institution with a strong track record in DEI. They present good data on the disproportionate impact of this indication as it relates to Black and Hispanic populations.
6-8: Responsive	4	• The modest description of DEI efforts is sufficient yet not very robust.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-14649
Title (as written by the applicant)	Extracellular Vesicle-Based Therapy for Corneal Scars
Translational Candidate (as written by the applicant)	Extracellular vesicles derived from stem cells for the treatment of corneal scars.
Area of Impact (as written by the applicant)	The candidate aims to restoring vision by reducing the need for corneal transplant and the associated blinding complications.
Mechanism of Action (as written by the applicant)	The therapeutic candidate is an extracellular vesicle (EV)-based therapy that could regenerate normal cornea tissue and reduce corneal scars without the need of corneal transplant. The unique population of EVs have anti-inflammatory and anti-fibrotic activities in addition to their regenerative property. The effect of EVs are likely acted via their microRNA cargo.
Unmet Medical Need (as written by the applicant)	Blinding complications such as infection, glaucoma and retinal detachment are associated with corneal transplant. By reducing corneal scars, vision will improve without the need for a corneal transplant, which will also greatly reduce the impact of global severe shortage of corneal tissues.
Project Objective (as written by the applicant)	Submit a pre-IND package
Major Proposed Activities (as written by the applicant)	• Identification of biomarkers and functional units of therapeutic candidate which will serve as basis of potency assays. • Optimization of route of delivery and dosing, pharmacokinetics and pilot safety. • Establishment of GMP compliant master cell bank and scalable extracellular vesicle purification process.
Statement of Benefit to California (as written by the applicant)	California is the most populated state in the USA. The number of residents with corneal scars may disproportionately increase as a result of multiple environmental and occupational factors. A safe treatment to restore vision is an important benefit to the people of California. Our project will further benefit California through the training of new stem-cell researchers, create more jobs, and attract funding from the federal government and investment from the private sector.
Funds Requested	$5,779,276
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	81
Median	85
Standard Deviation	11
Highest	92
Lowest	50
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	7
(1-84): Not recommended for funding	6

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/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	• There is an unmet need for non-surgical treatments for corneal scarring. Extracellular vesicles derived from stem cells could meet this need. This treatment would help to counter the worldwide shortage of corneal donor tissue for transplantation. • This product is a stem cell derived approach that has great potential to improve care of patient with corneal scars, a leading cause of corneal blindness. • This stem cell based product can potentially decrease risk and cost of therapy of corneal scars. • Patient care would be simplified compared with corneal transplantation, in that medication needed long term should be greatly diminished, as should risks of glaucoma, rejection, suture complications, etc... • Improvement over the current standard of care - corneal transplants - is an admirable goal. • Considering the advanced culture methods employed for production of the therapeutic EV used in the functional in vivo demonstration, the proposed EV therapeutic product has a high likelihood to advance developing stem cell technologies that would improve patient care with some significance. • With relatively limited manufacturing steps and likely quantities needed in the advanced methodology to culture, produce, and disposition the EV, the proposed therapeutic offers an impactful proposition to the patient community. • The proposal does present some risk in regard to value proposition to some health care providers. The product describes use of EV with description of in vitro assay development. Without a successful campaign to establish early characterization of the EV in vitro, there is risk in later-stage clinical development being dilated in time. The proposal does provide the appropriate attention with milestones to develop assays to support functional and identifying attributes during early stages of development.
No: 4	• The eye is a good target to test whether EV therapies can demonstrate efficacy because of local delivery and a well defined, accessible area to study effects. • The concept of a minimally invasive option for treating corneal scarring is an interesting one, however corneal transplants have been successfully performed in the US since the 1900s and they are not supply constrained. • Unclear as to whether there would be significant patient benefit. • The durability of any observed effect is important. The applicants state that optimally the EV could be administered weekly or monthly. This may not be more patient-friendly than a one time transplant that lasts 10-20 years. At the costs they indicate, monthly injections for one year would cost about the same as a transplant. Also, it would be harder to obtain insurance reimbursement and coverage for an office procedure than the surgical procedures. • The desired effect should be at least 3 months to be a useful, clinically practical treatment.
GWG Votes	**Is the rationale sound?**
Yes: 10	• As the community learns more about the potential for EV therapies, the rationale appears sound. The duration of effect should be maximized for better patient acceptance. • Extensive laboratory evidence exists for the role of this type of stem cell in corneal stromal healing and remodeling of scars. Extracellular vesicles (EV) derived from these stem cells appear to have similar properties to whole cells in promoting corneal healing. Storage and delivery of EV would be much more efficient and feasible than use of whole cells. FDA regulatory hurdles for a cell free product are lower than for cell therapy. • Immortalized cells will not directly be used, only their EV product, avoiding risks of transplantation of immortalized cell growth. • The proposed EV therapeutic has a sound rationale in regard to stem cell biology. The path towards manufacturing to support clinical efficacy results may be limited without a mechanism of action supported by an in vitro assay that may be used for early characterization to normalize dosing.

	• The proposed EV therapeutic is supported by the available in vivo model that demonstrated functional corneal repair from the early grade materials tested. Without an in vitro assay available to demonstrate a Lot of EV's general fitness, batch-to-batch variability of cells generated may emerge. The in vivo model would be less than ideal to demonstrate any future comparability. • The proposal is demonstrating a process for EV product development which has controlled advances from already demonstrated practices that achieved the remarkable corneal wound healing in vivo. Concerns around variability of product are expected to be mitigated to an extent by growth factors used in the culture of and in the derivation of stem cells. Literature is consistent in advancing to defined culture conditions to remove in vitro assay variability of EVs derived from undefined sources - "Foetal bovine serum influence on in vitro extracellular vesicle analyses." J Extracell Vesicles. 2021 by Lehrich BM et al.. • The proposal outlines efforts to also demonstrate the EV's immunomodulatory function with macrophages using a well developed assay. This does provide support for the profile of the target product in an in vitro setting. Of note, the macrophage cells present an ideal setting for an in vitro assay. The macrophage cells present many receptors that would trigger an inflammatory response from potential process contaminants or residuals that could also be evaluated to characterize product purity further. • The proposal outlined significant efforts to characterize EV's molecular identities with spectroscopy, including physical properties such as the particle count, size, structure of EV, and the surface profile, which all allow the team to effectively address specific agency concerns from earlier interactions (pre-pre-IND). This attention also included dedicated resources towards characterization of functionality with a novel in vitro cell-based anti-fibrotic assay. This assay includes aspects of migration that is past the discovery levels of development with proof of concept from the product provided. Continued success in these studies will only further support the growing narrative around corneal wound repair with purified EVs from stem cells. • The scientific rationale is reasonable. The concern is whether the effect size is clinically meaningful (magnitude and duration). • The reduction in scar area shown in Figure 3 shows a good result. Corneal opacity, the closest to a clinical endpoint, did not show much difference from the control (Figure 5). Gene expression can be highly variable so I did not find that data very convincing.
No: 3	• Unclear mechanism of action. • Data do not show convincing support for the indication or cell type.
GWG Votes	**Is the project well planned and designed?**
Yes: 9	• The design approaches all of the appropriate issues: mechanism of action, master cell line selection and GMP scaling, response and potency assays, purification processes, and safety and pharmacokinetic/biodistribution. • The program for the treatment of corneal scarring using EV derived from stem cells is constructed well overall due to advancements in the field demonstrating similar attributes for stem cell derived EVs for the treatment of tissue scarring. • The program's specific attention directed towards the development of an in vitro assay to characterize functionality further supports the well designed construction of the program. • The design of the proposed studies is acceptable. I think the efforts to develop a lyophilized version of the EV are worthwhile. • The use of an oncogene to immortalize the master cell bank should require monitoring of final EV product for this specific residual genetic element from the host cell DNA. A characterization method based on qPCR would de-risk many potential concerns that may emerge around the presence of the oncogene. An effort to quantify/detect trace amounts of the the sequence should have some qualification to support its potential use on final product disposition. If any amounts are detected, a biological assay that demonstrates the sequence is not stable when introduced and extended in culture of a permissive cell would be of utility. • Testing to disposition the GMP cell bank includes the expected compendia methods. But the plans should include adventitious agents testing for the bank when milestones are achieved which would trigger a clinical readiness and use of the bank without incurring delays. • This program is moderately process dependent to demonstrate conformance and would benefit with extra attention on developing a reference standard. A purified EV with an additional dimension of purification, e.g. gravity/density, that retains in vivo wound repair not only provides reference materials to measure against but also provides method development for generation of references.

	• In 2018, the FDA provided formal advice, with specific recommendations for manufacturing and dose justification. • There was a pre-pre-IND meeting in 2018. The project was at a very early stage, so FDA was only able to provide general feedback. I think FDA will want the dosing regimen in the animal studies to be relevant to the proposed clinical study. In the mouse study they plan to deliver up to two repeat treatments at an 8-week interval. This is different than what is outlined in the TPP. The applicants should study dosing in these mouse studies that will inform the design of their IND-enabling studies. • The applicants will not be able to do dose response in vivo and should focus on the in vitro tests to distinguish effects of dose level.
No: 4	• Use of the oncogenic antigen carries the risk of having T antigen in the EV - the applicants need to develop a test for this. • It is important that preclinical studies mimic the intended clinical program.
GWG Votes	**Is the project feasible?**
Yes: 13	• The outline of the project details sufficient access of equipment, facilities, and resources to complete the proposed activities. • Timeline is reasonable. • The PI is very experienced in corneal stem cell research and clinical applications. The PI is already well funded in this area and has received CIRM support for corneal epithelial stem cell product development. The other team members have appropriate expertise and specialized technique access. • Based upon the individual backgrounds intended to support the project and its deliverables, the proposed team does demonstrate the subject matter expertise to deliver on the expectations for corneal wound healing via EV products. They have demonstrated capabilities to reproduce corneal repair previously. • To support feasible GMP cell line generation, the project describes access to the GMP facility at a nearby institution for certification, expansion, and banking of a GMP-compliant stem cells. • To support feasible GMP drug product, the project describes appropriate access to a GMP facility for manufacturing activities. • The project and the proposed timeline appear technically feasible. Consultation on commercial feasibility should be considered to assure a commercial need for the product. • The proposed project plan is appropriately timed for the activities intended. Although the project does include development of an in vitro method to further test for functionality of the EV products, there was only evidence of progress on this campaign to date for one final product. • Without new donor derived EV product specific data it is difficult to appreciate any donor to donor variability the in vitro assay to support potency may present. • The project plan does describe contingencies to certify the existing stem cell lines available if the proposed GMP cell bank is demonstrated as inadequate. This will require consent from the eye bank that provided the corneal tissue for research purpose to establish the consent for therapeutic development. And although this approach is viable, it may present some limitations in the products profile. The comprehensive data, product specific history, and overall team experience does support some appreciation in their disposition of a "very unlikely event" around the failure of establishing a GMP-compliant corneal stromal stem cell bank in their initial attempts. • The risk section was fairly superficial and did not address real risks (they anticipated no actual problems).
No: 0	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13	• This product will be applicable to diverse populations. The use of this product will benefit currently underserved communities and potentially low resourced populations. • A non surgical treatment could be broadly available to patients. • Yes, the design of the program has overarching applicability to provide a product which would account for the influence of race, ethnicity, sex and gender diversity. They note that the potential for EVs to "differ amongst demographic groups from the donors they are derived from and the recipients who receive them" allows for potential advancements because "EVs possess notable differences in cargo (proteins, miRNA, etc), concentration, size, and functional effect (internalization, therapeutic response) based on age, race, and sex [25]".

	• Considering EV-based therapeutics presents with efficient production relative to other cell and gene therapy products, its ability to treat conditions that is intended to improve the quality of life of blind individuals does fit the profile of a product that would serve the unmet medical needs of the diverse CA population. • Based upon the applicant's understanding of evidence to suggest that "race, ethnicity, and age directly influence surgical outcomes of corneal transplants" as cited, the proposal does properly capture and represent the experience from the population. • Further DEI support is provided by the proposal citing other studies reporting race as a direct risk factor for graft failure where a cohort of patient's present a higher risk of failure versus another cohort. • This is an early stage proposal; additional information on incorporation of DEI principles would be expected as the development progresses. • This section was fairly good for an early stage project (i.e. it wasn't template language of existing programs). However, I remain concern about the needed frequency of doses. For many people, frequent doctors visits are burdensome.
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	2	• Good data and institution with strong, demonstrated track record of DEI in a clinical setting. • With the potential of cost savings there is a likelihood to reach and treat more underserved members of the community.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-14710
Title (as written by the applicant)	AAV Gene Therapy for Treating Congenital Hereditary Endothelial Dystrophy (CHED) associated with Biallelic SLC4A11 Mutations
Translational Candidate (as written by the applicant)	The therapeutic candidate is a recombinant AAV vector with single-stranded cDNA encoding the wild-type human SLC4A11 protein.
Area of Impact (as written by the applicant)	The candidate is for treatment of congenital hereditary endothelial dystrophy (CHED), an orphan disease associated with congenital corneal opacification.
Mechanism of Action (as written by the applicant)	The therapeutic candidate introduces normal copies of human SLC4A11 gene into the diseased corneal endothelial cells to compensate for loss of function pathologic biallelic SLC4A11 gene mutations, thus restoring the production of the defective or missing SLC4A11 protein and reverting the disease phenotype.
Unmet Medical Need (as written by the applicant)	Corneal transplantation is the only treatment for children with CHED. However, pediatric corneal transplantation is associated with risk of intraoperative and postoperative complications, including higher rates of transplant rejection and failure.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Studies in Mouse Disease Model to Determine Dose and Dose Schedule Optimization • Manufacturing of GMP-like Candidate for Pilot Safety Studies • Early Safety and Toxicology Studies
Statement of Benefit to California (as written by the applicant)	If successful, this project will be the first AAV gene therapy for an anterior segment disorder to enter a Phase I clinical trial. The project will demonstrate CIRM's commitment to supporting gene therapy trials for blinding pediatric anterior segment disorders that affect children in California and globally. Experience obtained via this project, which is California-based, will accelerate future efforts to make cell and gene therapies available to the people of California.
Funds Requested	$4,338,166
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: 80

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

Mean	80
Median	80
Standard Deviation	6
Highest	90
Lowest	70
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	5*
(1-84): Not recommended for funding	8

* 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	• The proposed product will treat congenital hereditary corneal endothelial dystrophy (CHED), a rare orphan disease in the US. This recessively inherited disease is much more common in the Middle East and South Asia. Current treatment with corneal transplantation during infancy is technically difficult, high risk, and limited by donor shortages in the regions with highest prevalence. • This gene therapy approach would provide an alternative to corneal transplantation, which carries risks, high care burden, and the need for repeated transplants. Transplantation also relies on availability of donor corneal tissue and trained surgeons. • The value proposition is reduced burden of post-treatment care. This improves health equity. • An additional value proposition is validation of the potential for gene therapy as treatment for other ocular inherited anterior segment disorders. • The proposed delivery method, intrastromal injection of the gene/vector, has great potential for treatment of other corneal dystrophies, particularly monogenic dominantly inherited corneal stromal and endothelial dystrophies. These are much more prevalent than CHED. • The innovative proposed route of administration could open gene therapy applications for other rare disorders. • This has potential for impact in CHED. However, the duration of effect will need to be significant for the value proposition to be practical.
No: 0	*none*
GWG Votes	**Is the rationale sound?**

Yes: 12	• Preliminary proof-of-concept data ex vivo and in vivo in a relevant animal model of disease and safety data via intended route-of-administration support clinical translation.
	• The direct intracorneal delivery of the SLC4A11 gene with an adeno-associated virus carrier (AAV-SLC4) is based on extensive preliminary studies.
	  ◦ In an SLC4A11 deficient mouse model, the gene therapy reversed cornel edema and endothelial cell loss.
	  ◦ HEK cells were successfully transduced by the gene therapy.
	  ◦ Corneal delivery of the therapy by intrastromal injection was demonstrated in dog, rabbit and human corneas ex vivo.
	  ◦ Toxicity was not seen in human corneal endothelial cells, human donor corneas or in canine, rabbit or feline models.
	• Ophthalmologic indications have been fraught with failures of candidate cell and gene therapies. The rationale expressed in the proposal appears sound but, thinking through the practical application - if the therapy requires multiple injections, this may be a concern.
	• This proposal includes strong preliminary data with an approach that treats a new structure in the body.
	• The proposed gene therapy approach is relevant for the proposed monogenic ocular disorder.

No: 1	• It's not clear the applicant will adequately score what constitutes controlled gene delivery, including gene expression, within the targeted cornea tissue.
GWG Votes	**Is the project well planned and designed?**
Yes: 5	• The proposal includes a stepwise plan for exploring dose ranging, developing vector potency assays, immune in vitro efficacy assays, manufacturing feasibility, toxicity studies, and preparation for FDA meetings. • Overall, yes. However, the toxicity and immunological aspects of the grant need to be refined based upon additional feedback from a regulatory specialist or from the FDA. • The experiments appear reasonable. Unfortunately, the applicant's request for an INTERACT meeting with FDA may not be granted as the FDA/CBER Cell Therapy group is currently in a backlog.

	• Some of the proposed studies may not be relevant for injecting rAAV into an avascular structure of the eye.
No: 8	• Preclinical studies are not well designed to address major issues that will be of significance for FDA review. For example, evaluation of the gene therapy in a model with pre-existing antibodies is no longer needed for indications that use intra-ocular administration. The impact of pre-existing anti-AAV capsid antibodies seems to have now been addressed both pre-clinically and, more importantly, clinically with other ocular programs. • The strategy for an INTERACT meeting and pre-IND meeting needs some work. Importantly, the design of the pivotal toxicology study to support the IND would not be discussed at the INTERACT meeting. The applicant could get concurrence that rabbit was an appropriate species at an INTERACT meeting. A 6-month pilot safety study would not need to be completed prior to a pre-IND meeting. • The applicant is missing the opportunity to learn more about their route of administration and efficacy in the rabbit toxicity study. • The applicant needs a clearer approach to controlling and measuring the transgenic protein's functional rescue of membrane transport in corneal cells with biallelic SLC4A11 mutations. Knowing the extent of functional, cellular rescue will aid in the interpretation of studies of transgene delivery and efficacy. • The applicant should propose studies characterizing the potential impact of the extracellular environment in the cornea on transgenic SLC4A11 function. • Key delivery aspects are not sufficiently explored or planned, perhaps as a cost of focusing on immunogenicity and systemic distribution studies. • The transduction efficiency of the vector is not discussed adequately in the proposal. • The applicant is leveraging data from other development programs, i.e., different diseases, different genes; the applicant has minimal data with the lead candidate. • The team appears to have limited experience with rAAV production and conducting GLP gene therapy toxicity studies.
GWG Votes	**Is the project feasible?**
Yes: 11	• The proposed milestones should be achievable assuming successful manufacturing capability. • There are several unfilled positions that are critical to the execution of the proposed experiments. • The team is strong, but the proposal needs more input from regulatory specialists. • Yes. Resources at the partner institutions are outstanding. • It's not clear that an INTERACT meeting is needed.
No: 2	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13	• The applicant institution has a DEI program. This program is early stage and will need additional information as it progresses. • Validation of the route of administration has the potential to lead to other gene therapies for more prevalent inherited disorders of the anterior segment of the eye. • The PI's natural history studies found more severe disease in male than in female patients. This will be explored in the animal models. • The applicant will work with their institutional community engagement program throughout the clinical trial phase. • The proposed product will address a condition which occurs in diverse populations. • More attention will be needed at the trial recruitment stage, but the plan is sufficient for now. • The applicant appears to embrace DEI values.
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: 7.0

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	• The proposal includes good data, and the institution has a strong DEI track record in clinical trials. • The DEI enhancement strategy reflects a well-defined intent. • The applicant plans to integrate the perspectives of people from marginalized groups in trial design and planning. • The applicant plans to partner with trusted community organizations in designing data collection and engagement procedures for a Phase I/II trial. • This gene therapy could address children's unmet medical needs world wide.
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.

Thirteen scientific GWG members scored this application. Eight GWG members scored from 70-80; five scored 85 to 90. All scoring panelists agreed that the project had the significance and potential impact required for a CIRM project and upheld principles of DEI. Nearly all thought the project had a sound rationale and the activities were feasible. All comments on the preliminary data were positive; one supportive reviewer described the preliminary data as "extensive" and noted the applicant's completed studies in a relevant preclinical mouse model and corneal tissues from humans, dogs, rabbits, and cats.

The panel was divided on whether the proposed project plan was sufficiently sound. For the most part, supportive panelists agreed with the majority that the regulatory strategy needed work. While the majority wanted to see the project plan revised with fuller characterization of the product and more input from FDA or a regulatory consultant, reviewers who scored 85 or higher found the project meritorious despite weaknesses in the current project plans. This support appeared to be driven by the value proposition - supportive reviewers noted that the proposed gene therapy would be an alternative to corneal transplantation, which requires donor tissue and trained surgeons, the disease indication has a high prevalence in some underserved racial/ethnic groups, the project could validate the potential for gene therapy for more prevalent inherited ocular disorders, and the applicant is testing a novel delivery method for gene therapies.

Application #	TRAN1-14620
Title (as written by the applicant)	Development of a Gene Therapy for the Treatment of Arginase Deficiency - Translating from Proof of Concept to Pre-IND Meeting
Translational Candidate (as written by the applicant)	Adeno-associated viral vector serotyped for hepatic tropism to express arginase 1 in hepatocytes
Area of Impact (as written by the applicant)	Developing a therapy for Arginase Deficiency
Mechanism of Action (as written by the applicant)	The proposed therapeutic candidate is a virus engineered to produce the missing arginase protein in patients with Arginase Deficiency. The virus will be delivered intravenously and target the liver. Successfully restoring arginase expression in the liver will resolve the elevated arginine levels and abnormal arginine metabolites that cause abnormal function of neurons and oligodendrocytes in these patients.
Unmet Medical Need (as written by the applicant)	Arginase Deficiency results in progressive cognitive decline, often with seizures, loss of developmental milestones, and loss of mobility in children, who frequently become wheelchair-bound. Therapy today is dietary only, which is minimally effective. This proposal is to bring an effective gene-based therapeutic approach to IND.
Project Objective (as written by the applicant)	Pre-IND meeting and clinical trial planning
Major Proposed Activities (as written by the applicant)	• Generate and characterize clinical-grade adeno-associated viral vectors for expressing arginase-1 (ARG1) in liver. • Characterize safety profile of intended clinical product via a toxicology study with clinical-scale lot. • Develop protocol, Investigator's Brochure, and consent materials in preparation for early phase clinical trial. • Develop Pre-IND Meeting Package for FDA submission.
Statement of Benefit to California (as written by the applicant)	Genetic-based causes of intellectual disability, like Arginase Deficiency, are a more common occurrence than is appreciated by the general public. There are many families in California living with these conditions. Our team will collaborate with partner organizations and vendors in our state, including the ARG1 Deficiency Foundation, and patient caregivers to achieve our endpoints. Our efforts will support identification and inclusion of California families in the pursuit of a therapy.
Funds Requested	$4,771,122
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: 80

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

Mean	80
Median	80
Standard Deviation	5
Highest	90
Lowest	70
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	2
(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: 13	• ARG1 deficiency is a devastating disease with no curative treatment. This application definitely addresses an unmet clinical need. • Consistent control of ARG1 deficiency remains an unmet medical need, especially in the pediatric patient population. • The proposed product replaces the deficient enzyme and could be an improvement to standard of care. Sufficient reduction in plasma arginine levels in patients has been difficult to consistently achieve. • The proposed product offers a one time treatment and potential cure. The standard of care carries the burden of chronic compliance to specific dietary restrictions as well as the need for repeated ammonia diversion therapy, which can be toxic. • A gene therapy for ARG1 deficiency will definitely be a life changer for patients and greatly improve their quality of life. • This rAAV product may become a regenerative, in vivo, molecular medicine. Based on the in vivo results provided and the proposed facility for product development, the applicant will have a safe approach to clinical testing. • The proposal provides an impactful proposition for patients based on the in vivo preliminary studies. • ARG1 deficiency requires very heavy and costly palliative treatment that only alleviates some symptoms. Patients require high levels of care. Thus, better treatments will have major value for patients, their caregivers and health care providers. • The applicant proposes a tropic approach for gene delivery of an active AGR1 with liver-specific expression. Restoration of ARG1 levels to ~10% normal levels of hepatic arginase protein are likely achievable in the clinical setting with this program's design. • The development of a gene therapy would greatly improve patients' quality of life. Of note, the proposed approach might not represent a cure since diagnosis is often obtained after first symptoms and thus potential irreversible neuronal damage. • Yes, but the approach might not provide a cure due to the late diagnostic for this condition. However, the approach proposed by the applicants can be used for a broad number of rare disease and, thus, the impact of this proposal could go beyond ARG1 deficiency. • Overall, yes, but there is some risk with regard to the value proposition. The proposal does not include adequate plans for characterizing enzyme activity and rAAV infectivity in vitro. Without thorough early characterization of these product attributes, the project may face delays in CMC and clinical development. Key CMC attributes unaddressed during early stages of development generally require resource intensive studies later, to address every gap with in vitro assays with long lead times.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• This is a very straightforward concept, i.e., replacing defective ARG with the wild type gene to provide missing function. There are no major conceptual or even technical challenges associated with this proposal. • AAV are currently used in a broad number of trials targeting genetic diseases originating from the liver. Early trial results for clotting factor deficiency have established safety and provided support for efficacy. • The preliminary data provided from animal models are convincing. They clearly show that the disease progression can be stopped using this gene therapy approach. • The rationale is supported by successes of previous enzyme replacement therapies, as well as several ongoing clinical trials of gene therapies for metabolic liver diseases. • The levels of expression and enzyme activity for this construct have shown suitability based on validated animal models that recapitulates the disease, and scientific understanding of rAAV vectors. Characterization of ARG1 expression and activity in vitro during this project would support seamless translation. • Yes. The preliminary studies using validated animal models support gene delivery, expression, and ARG1 activity in the targeted hepatic tissue. These data support further

	development, i.e., to optimize timing of dosing, dose response and durability of response. • In the group's published article (Mol Ther. 2014), they demonstrate that a similar vector with codon optimized ARG1 shows arginase expression. These data support the rationale for the proposed project. • The combined experience of the team and the rAAV production facility will support efficient development of in vitro assay(s) for product characterization. • The facility's experience and its history of results also provide substantive support for clinical grade production of the proposed rAAV drug product. • Overall, yes, but long-term maintenance of arginase expression is not yet established. This is likely to be major point of discussion with regulators. AAV do not integrate into the genome, and their maintenance can decrease in dividing cells over time. This potential limitation is still debated in the field, and could be more problematic in pediatric patients. • Animal data clearly show that the proposed gene therapy stops disease progression but does not rescue all the phenotypes induced before treatment. In ARG1 deficiency, injury likely begins during early post natal life (if not earlier). This early damage might not be repaired by this gene therapy approach.
No: 1	• The potential impact on patients who are born with microcephaly is unknown. This needs to be studied in a better animal model.
GWG Votes	**Is the project well planned and designed?**
Yes: 4	• The planned experiments support achievement of the project milestones. In addition to patient outreach to define endpoints, consultation with the FDA on the critical path initiative may be informative.
No: 9	• This is a well-constructed program overall but key details are missing. The program properly leverages quality expertise in rAAV production and disposition to support pre-clinical and future clinical studies. The team has demonstrated a strong understanding of the disease indication and its treatment. However, the plan for pre-IND needs work. • The CMC package is not well-developed in terms of delivering a product for a phase 1 trial. • No justification has been provided for the design of the proof-of-concept study, including day of dosing, duration or rationale for success criteria. • Proposed doses for proof-of-concept and safety studies appear to be benchmarked from an industry study rather than prior experience in ARG1 knock out mice. • Consideration of viral transduction efficiency in human as compared to murine hepatocytes may further inform dosing. • The applicant should consider bracketing the clinical dose in the toxicity study - i.e., the highest dose in the toxicity study should be higher than the highest intended clinical dose, if technically feasible. At least, it should be higher than the effective dose in mice. • Quality oversight was not adequately addressed. • A viral capsid production threshold of 20% seems to be a very low bar for current industry standards. • The levels of expression and enzyme activity for this construct have shown suitability based on validated animal models and scientific understanding of rAAV vectors. Characterization of ARG1 expression and activity in vitro during this project would support a seamless long-term clinical CMC rationale. • Defined, product-specific characterization assays to quantify infectivity, ARG1 expression, and activity are needed to support and demonstrate control of the product at later stages of development into commercialization. • CMC gaps in characterization are to be expected at this stage of development. But these allowances to facilitate development may present delays in industrialization of a clinically proven therapeutic. Though not required for disposition at earlier stages, the availability of the assays in a matured state allows them to elevate to product disposition when needed, or when requested by the agency. • The potential immunogenicity of the transgenic protein in patients is not addressed. • The applicant needs to better elucidate the natural history study. • To optimize the success of Milestone 4, consideration should be given to FDA's published guidance on Natural History Studies for Rare Diseases (2019). • It is unclear whether Milestone 4 is a longitudinal assessment of subjects over 2 years. The study may represent an opportunity to study participant MRIs as potential biomarker of activity. • The project will start relatively promptly with clinical grade vector production within a couple of quarters and conclude with overlapping milestones 3, 4, 5, and 6 during the 1st

	quarter of year 3. Based on this, the project plans demonstrate an urgency commensurate with CIRM's mission, but also raises concerns around design of product development plan around GLP studies with grade of vector. • There is potential to accelerate the regulatory process, as a full clinical protocol, IB, ICF and pilot toxicity study would not be needed to support a pre-IND.
GWG Votes	**Is the project feasible?**
Yes: 12	• Based on the preliminary data provided and the quality/expertise of the applicants, the project seems highly feasible. • The proposed team members have the subject matter expertise to deliver on expectations. • They have longstanding ties with the ARG1 Deficiency community and will appropriately attend to community needs for their early phase program. • The team has access to all the resources to conduct the proposed activities. Specifically, the applicant has access to clinical grade vector representative of their discovery materials, access to the animal models for in vivo characterization of the clinical vector, and access to the clinical site at the institution. • Potential risks have been identified and mitigation strategies seem appropriate. • The project plan appropriately addresses and mitigates risks in vector production. • There are risks within the planned CMC milestone #1 to evaluate/assess expression in vivo in adult mice of the rAAV drug product. The applicant mitigates some concerns with a deep characterization of vector integration. • As outlined in the proposal, the pieces are in place to complete the milestones. • Resources are adequate to conduct the proposed activities. • The milestones should be achievable.
No: 1	• Concerns about immunogenicity are not addressed. • This product's impact may be limited in clinical outcome, especially in individuals born with microcephaly.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13	• The proposal presents an evolved approach to treat a disproportionately affected population in CA. They note the prevalence frequencies for the differing ethnic groups and conclude, "[a]s Latinos are the largest racial and ethnic group in California at 39.4% we will be making a particular effort in meeting the unmet medical needs of this group within our diverse California population." • The overall study plan and design considered the influence of race, ethnicity, sex, gender, and also age diversity in the development of this therapy. • The potential impact of sex is being addressed preclinically. The potential influence of race and ethnicity are minimized by the limited prevalence of the disease. • The application reflects an appreciation of the burden on traditionally underserved and underrepresented communities. • The application reflects specific intent to reach out and engage a diverse population. • The project intends to use both male and female mice.
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	• The application includes well-selected data on demographics. • This is a great institution with regard to strong DEI capabilities in clinical trials.

		• The application includes a good assessment of impact related to research approaches.
6-8: Responsive	3	• The application reflects specific intent to reach out and engage a diverse population. • The applicant recognizes the importance of involving patients from groups experiencing ethnic and racial disparities in the development of genetic therapies. • The application reflects an appreciation of the burden of disease on traditionally underserved and underrepresented communities. • The applicant is aware that lower-income families with a child with Arginase Deficiency bear a disproportionate burden of disease. • The applicant ties the predicted incidence among CA's ethnic groups to their priority to serve these communities stating that they "will be making a particular effort in meeting the unmet medical needs." • The applicant looks forward to a clinical trial. They expect to learn more of patient caregiver challenges and opinions about a gene therapy treatment for Arginase Deficiency in their Milestone 4 studies, and plan to incorporate these findings into their plans for a clinical trial. • The planned studies will use both male and female mice.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN4-14726
Title (as written by the applicant)	Development of a low-cost, clinical-grade iPS maintenance medium for enabling stem cell therapy manufacturing
Translational Candidate (as written by the applicant)	An iPS cell maintenance medium designed to reduce stem cell GMP manufacturing costs and risk.
Area of Impact (as written by the applicant)	This product addresses scale-up manufacturing, by being lower-cost ($300/L) and requiring fewer passages per week (1-2 as opposed to 3-5).
Mechanism of Action (as written by the applicant)	This product underwent extensive empirical optimization and alternative component screening, focused on reducing cost, maintaining iPS cell pluripotency and robustness, and enabling weekend-free, minimal-passage stem cell culture. This included the implementation of a novel thermostable variant of a growth factor that enables improved medium stability and half-life in culture. These changes enable lower-cost cell culture and fewer passages, minimizing manufacturing errors and contamination risk.
Unmet Medical Need (as written by the applicant)	iPS cell-derived therapy candidates are quickly emerging to target a wide range of diseases and disorders. Scale-out (autologous) and scale-up (allogeneic) processes will require cost-effective media with minimal user handling to be a widely applicable technology. This product is engineered for this.
Project Objective (as written by the applicant)	Readiness for transfer to manufacturing
Major Proposed Activities (as written by the applicant)	• Manufacture 300 L of analytical QC-validated product via cGMP methods for clinical application. • Evaluate cGMP-grade product for proliferation, pluripotency, karyotype, and differentiation. • Evaluate cGMP-grade product in large-scale clean room production for proliferation, pluripotency, karyotype, and differentiation.
Statement of Benefit to California (as written by the applicant)	This application is focused on enabling cost-effective scaled manufacturing of iPS cell-derived therapeutic technologies, which will benefit all demographics of the nearly 40 million people in California who, at some point, may suffer a condition that would benefit from such technologies. Ease of scaled cell manufacturing enables competitive therapy development and more affordable solutions. It also increases the number of cell therapy producers and associated businesses and jobs in the state.
Funds Requested	$999,848
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: 80

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

Mean	79
Median	80
Standard Deviation	9
Highest	90
Lowest	55
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	5*
(1-84): Not recommended for funding	9

* 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: 10	• The proposal is designed to address key bottlenecks in the commercialization of a new clinical-grade maintenance medium: cGMP manufacture with established and experienced partners, robust evaluation of performance, and scaled clean-room cell manufacture. The resulting product specification, formulation and performance metrics will enable low-cost, low-risk expansion of human iPS cells for clinical-grade manufacturing of stem-derived technologies, benefitting California's nearly 40 million residents that someday may benefit from affordable iPS cell-derived therapies. • GMP production of what appears to be the best currently available medium for expansion of clinical grade human iPS cells would be of substantial practical benefit for multiple projects in regenerative medicine. This appears to be a valuable service to the entire community working on pluripotent stem cell-derived products. Should impact multiple unmet medical needs that can be addressed by cell therapy products based on differentiation of human iPS cells. • Yes and no. Better media for cell therapy GMP production are sorely needed, especially for iPSCs. The specific requirements for each cell line may differ based on not only medium, but also growth conditions. • Strength in the application is for iPSC development around media but may not address other bottlenecks in iPSC development. • In this proposal, they aim to produce a clinical grade media that can enable lower cost, lower-risk expansion of human iPS cells for clinical-grade manufacturing of stem-derived technologies. While if successful, it has potential to address one of the bottlenecks, it does not address other challenges related to iPSC development and in some ways minimizes them. • This product could contribute to acceleration through addressing some of the development barriers of iPSCs, but as a stand-alone, unclear how great impact will be (cost, multiple passages, "weekend-free" passaging). • Only partially so. The main bottlenecks (or high price) for iPSC therapies are not because of lack of media for iPSC maintenance.
No: 4	• Value proposition is to not have to validate the medium for each development program. • Does not address the overarching concerns of all the potential bottlenecks; the value proposition, as such, may not have significant impact.
GWG Votes	**Is the rationale sound?**
Yes: 11	• The components of the media are well described and justified. The project is based on a media that has been shown to support iPSC maintenance and propagation. • Concerns around specific focus on media is a sound rationale given the value proposition to the community. • The team already has developed an excellent serum- and xeno-free medium for iPS cell expansion, optimizing each of the key ingredients. They have shown it works for multiple iPS lines. The development of GMP grade medium is a logical next step. • The engineering of a stable growth factor, in particular, enables culture of iPS cells without the need for daily medium changes, which significantly increases convenience and reduces cost of cell production. It is the labor cost, rather than the cost of components, that is most important in the economic value proposition. • Yes, this appears to be the case: project aims to directly address these bottlenecks for the usage of the product to produce consistent, low-cost clinical grade iPS cells. • A concern is the applicability of the project across the different types of production methods. • The rationale is sound, but in some ways minimizes challenges of iPSC bottlenecks (safety of reprogramming method, donor-to-donor variability, cryopreservation, viability post-thaw). The applicants discuss but don't address the regulatory challenges.
No: 3	• Work has been done. • Unclear as to value proposition or innovation of the medium.
GWG Votes	**Is the project well planned and designed?**

Yes: 13	• The plan and design are appropriate for the early-stage development of a GMP grade medium. • Nicely staged from initial formulation and validation at small scale to transition to large scale culture under GMP. • Project plan is tightly constructed and should be completed within the 24-month timeline. • Considering the value proposition, the project is well planned. • Logical progression. • The goal is to make GMP/clinical grade media. The steps towards this are well described, but the quality systems, contracts and documentation needed are not sufficiently described.
No: 1	*none*
GWG Votes	**Is the project feasible?**
Yes: 13	• The technologies exist to determine if the program meets the milestones as defined. • Scientific proof of concept already fully established. • PI and staff are excellent. Good collaborations for manufacturing and for testing at large scale in an appropriate cleanroom environment. • The project is feasible but the application lacks some detail for QP, documentation, etc..
No: 1	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12	• Sufficient number of iPS cell lines are included from individuals representing both sexes, different races and ethnicity to ensure against the extremely unlikely possibility that cell culture medium for iPS cells would perform variably as a function of those parameters. • Project is agnostic as to the specific medical need or population(s) that would most benefit. The burden to take DEI factors into account for medical applications does not rest with the teams making the basic "nuts and bolts" that can be used for any project involving iPS cells, so long as they perform equally well with cells from any individual. • Acknowledges difficulties in being fully inclusive due to cost and time but also attempted to address DEI. • Acknowledged challenges. • Yes, both the data forming the foundation for this proposal, and the actual proposal takes this into account. • If a product is generated it serves a diverse California population. • Some concerns around attention on DEI.
No: 2	• Not much specific information to support the principles of DEI with their product was given. As noted, the cost of performing experiments on cells from a number of diverse individuals is prohibitive at this stage.

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: 6.0

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	• Good data analysis and thoughtful approach to development that factors in DEI framing for patients. • The applicant's approach will appropriately bring diverse and inclusive perspectives from the population that will benefit from the proposed product. Activities match the needs of the project.

		• There is adequate discussion on what is currently known about demographic disparities in the population that will benefit from the proposed product. • Applicant states outcomes will inform the development of the product by way of community engagement which can be implemented across many stages of a proposed project, including design, preliminary data collection, development, analyses, and publication/dissemination. The goal here is to highlight the value of scientific outreach to better serve the unmet medical needs of the diverse California population.
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.

This application was scored by 14 GWG panelists. One panelist scored 55, eight panelists scored 75 to 80, and five scored 85 to 90. Reviewers who recommended the application for funding thought that the development of a clinical grade iPS medium would have significant value. Some reviewers who recommended the application acknowledged that the product would not address other bottlenecks in iPSC development but thought that it was unrealistic to address all bottlenecks, and that the application tackles one of many – a serum-free chemically-defined medium as a tool for manufacturing of iPS cell-based therapies. In addition, a reviewer who recommended the application also acknowledges every developer may have their own custom medium, but this application is about offering a novel “base cell culture medium” with all customizations achieved by the addition of different supplements, as is true for every product/process in the cell therapy field. Reviewers agreed that the plan is logical, the timeline is reasonable, and the scientific proof of concept is established. Reviewers who recommended the application largely agreed that the project acknowledged the limitations of addressing DEI at this stage and for this type of product, though one reviewer thought the applicants could have provided more information specific to their product.

Application #	TRAN1-14714
Title (as written by the applicant)	Noncoding RNA drug TY1 as a therapeutic candidate for scleroderma and systemic sclerosis
Translational Candidate (as written by the applicant)	Modified synthetic noncoding RNA molecule
Area of Impact (as written by the applicant)	Systemic Sclerosis
Mechanism of Action (as written by the applicant)	The mechanism of action of TY1 is to improve outcomes in systemic sclerosis through attenuation of tissue injury, inflammation, and fibrosis through direct targeting of cell stress pathways including stress-induced MAP kinase signaling (e.g. ckn1a/p21).
Unmet Medical Need (as written by the applicant)	Systemic sclerosis is an incurable disease with no effective therapeutic management strategy. In this proposal we seek to develop an orally-administered engineered RNA therapeutic with remarkable disease-modifying bioactivity in in vitro and in vivo preclinical models.
Project Objective (as written by the applicant)	The objective to convene a pre-IND meeting.
Major Proposed Activities (as written by the applicant)	• Product characterization • Preclinical studies assessing dose, toxicity and biomarker development • Regulatory planning
Statement of Benefit to California (as written by the applicant)	The target indication is systemic sclerosis, a crippling, incurable, and the most lethal rheumatic disease (30% mortality rate over 10 years). Systemic sclerosis disproportionately afflicts disadvantaged populations (women, Blacks and Latinos, and Native Americans). Because the therapeutic candidate is universally applicable, the societal benefits of success here are expected to be profound.
Funds Requested	$2,796,329
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	74
Median	75
Standard Deviation	10
Highest	85
Lowest	55
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	3
(1-84): Not recommended for funding	10

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: 10	• There is a need for new therapies for patients with scleroderma and systemic sclerosis. Novel RNA therapies have been demonstrated to be safe and effective. • Diffuse scleroderma remains an unmet medical need and this product has the potential to significantly improve patient outcomes in a disease that leaves its patients hopeless. • Systemic sclerosis (SSc) is an autoimmune connective tissue disease with high mortality (>30% at 10 years) and there is no drug approved for the treatment of SSc. This product, if successful, will be likely to impact the treatment of SSc. • SSc afflicts <200,000 Americans, most of whom are women between the ages of 30 and 50. The reported prevalence of SSc is ~10-20 per 100,000 individuals, with an annual incidence estimated at 1-2 per 100,000 individuals in Europe and North America. Thus, the proposed product will have a moderate level of impact or influence.
No: 2	• The potential impact is difficult to determine due to the lack of relevant animal models that mimic clinical disease.
GWG Votes	**Is the rationale sound?**
Yes: 8	• With the data developed in-house, it appears that the product may significantly impact the burden of disease in animal models. • In the animal models exhibiting manifestations of the disease, both intravenous and oral administration demonstrated favorable outcomes. • Data is supportive from animal studies to decrease fibrosis. • Preliminary data suggest the anti-inflammatory and anti-fibrotic properties of the therapeutic candidate TY1 in multiple murine disease models. The non-specific effects of this therapy lead to concerns regarding the lack of a known mechanism of action by which TY1 modulates inflammation and fibrosis. • The concept for the drug product is well-researched and is feasible for a commercial product. • In preparation for the pre-IND meeting, more information will be needed about the characteristics of the final drug product. • One gap in the information is a discussion of potential for immunogenicity of the product and possibility of repeat dosing. This gap may be ameliorated if the characterization and release testing of the drug product demonstrate the integrity of the micelles.
No: 4	• Preliminary data suggest that TY1 has the potential to decrease fibrosis. Unfortunately, the fact that the mechanism of action has not been described reduces the enthusiasm for this application. • The mechanism of action is not clear. • The use of oral formulation has not been tested for shRNA. • The route of administration may not be relevant to the disease. • TY1 is an engineered derivative of the RNA molecule secreted by cardiosphere-derived cells. The proposal cites two papers which claim that the adult heart has cardiac progenitor cells, and these cells have stem cell properties. Data supporting the existence of cardiac stem cells have recently been called in to question. Furthermore, cardiosphere-derived cells have been tested extensively in clinical trials in Europe for treating myocardial infarctions and have failed to demonstrate efficacy. Therefore, the foundational papers supporting this approach are questionable. • The applicants should review the signaling pathways studied in Figure 2g and reassess possible implications for mechanism of action. • The applicants do not sufficiently justify how the models studied in Figure 4, Figure 6, and Figure 7 are relevant to or suitable for modeling SSc pathogenesis. In addition, using BNP level alone may not be sufficient to characterize heart failure. • The data do not provide strong evidence to support the development of the product. Specifically, the model studied in Figure 10 is the most suitable for studying SSc-induced fibrosis. However, the improvement observed after TY1 treatment in this model is limited.
GWG Votes	**Is the project well planned and designed?**
Yes: 4	• The proposed plan timing appears acceptable for fulfilling the stated milestones.

	• The applicants should provide more information on the analytical methods that will be used to characterize and release the product. This includes immunogenicity testing and biomarkers if not routinely utilized. • A raw materials/reagents qualification plan should be developed. One of the required components of the product is not supplied today as a GMP reagent. The applicants should consider the steps, timing and costs to develop a GMP-source of this component. • The project is appropriately planned with testing of oral TY1 in a second model of SSc. Studies in a large animal model, such as pigs, are also recommended. • It may be difficult to translate the proposed method of encapsulation into the clinic, because this method has not been used in patients yet.
No: 8	• The applicants haven't sufficiently considered the pharmacology and toxicology studies that are needed for supporting a novel formulation. • The rationale for the relevance of animal models of disease to support the proposed indication is not provided. • The amount of time and materials needed to prepare CMC materials to support preIND enabling activities may not feasible.
GWG Votes	**Is the project feasible?**
Yes: 9	• This project can be finished in the proposed timeframe. • This team is qualified to perform the proposed project. • Yes, to a point, however there is no information on moving beyond research-grade material. For serious consideration for treating humans, a plan and budget for providing GMP-grade material is needed. • The team should be supplemented with a quality compliance consultant to address a Quality Management System for the production, testing and documentation of the development of the product. • The team is optimistic with risk identification. The team should assume that there will be challenges with developing and qualifying test methodology.
No: 3	• The team should add details concerning how they will characterize the product, especially with the novel route of delivery, to minimize regulatory challenges.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12	• The proposal takes into account the diversity of the patient population to support a welcoming environment for all patients. The nature of the product may make healthcare provisioning easier for patients of all backgrounds. • The impact of this therapy on underrepresented populations is well described and highly relevant because scleroderma is more prevalent in African Americans. • This short RNA product should be accessible to people from diverse race, ethnicity, sex and gender.
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	• The applicants provide excellent demographic data with race and age statistics of prevalence, combined with data around disease impact with a vastly disproportionate impact for young, black women. • The applicants also provide a good analysis related to the financial burden of anti-fibrotic agents, citing $1.6M cost for

		one patient year of life added. This disproportionally impacts patients with limited income. • The applicant's institution has a good track record around DEI in clinical patient populations.
6-8: Responsive	1	*none*
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-14688
Title (as written by the applicant)	High-titer bifunctional lentiviral vector to reduce costs and increase access for Sickle Cell Disease gene therapy
Translational Candidate (as written by the applicant)	Autologous CD34+ Hematopoietic Stem and Progenitor Cells from Patients with Sickle Cell Disease Transduced with UV1-DS Bifunctional Lentiviral Vector
Area of Impact (as written by the applicant)	Sickle Cell Disease will be treated safely and effectively at reduced cost
Mechanism of Action (as written by the applicant)	Efficient modification of the blood-forming stem cells from Sickle Cell Disease patients with the high titer UV1-DS lentiviral vector will lead to expression in red blood cells of 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. The high titer and efficiency of the vector will reduce costs and help to improve access.
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 • Develop GMP-compatible methods to produce the UV1-DS-modified autologous hematopoietic stem cell Drug Product and produce 1 demonstration lot • 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 100,000 across the U.S.) suffer from Sickle Cell Disease. 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	$3,580,750
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	7
Highest	80
Lowest	60
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: 5	• Sickle cell disease (SCD) has remained an unmet need. This proposal aims to reduce costs to improve patient access to genetic therapies for SCD.
No: 8	• Given that several genetic therapies for SCD are going to be available in the commercial sector soon, one of the main issues that needs to be addressed is the cost barrier to accessing these therapies. The applicants have rightly mentioned that the high prices in the range of $1-3 million may limit the availability of these therapies and bringing these costs down is imperative to making such therapies available widely. However, the proposal does not present a significant case to support the applicant's assertion that bringing down the vector manufacturing cost is sufficient to reduce the commercial cost of manufacturing. The commercial cost of such therapies is generally not based on the cost of manufacturing but on the opportunity for getting the maximum return on investment. This leads to a concern that this genetically modified product may have a limited impact in a competitive field dominated by several industry and academic interests. • A majority of capital expense for ex vivo cell and gene therapy is in the cell processing portion of the product. Even though this project plan represents the appropriate direction to address the vector aspect of value, a more impactful value proposition would ideally address reductions in cell processing costs to a significant extent. The vector expenses saved from the proposed advancements, though significant, would likely reside at the margins of costs savings at scale in an industrial setting where recombinant LV is a drug substance in an ex vivo cell drug product process. • 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). The investigators present understandable data in support of LV gene transfer and the safety of such methods. But when other highly efficient and targeted modalities are available, promoting a random insertion-based LV gene transfer method seems like an out-dated approach. By the time the proposed approach reaches the clinical stage, alternate therapies which are much more targeted will likely be approved and marketed. In sum, this proposal is unlikely to accelerate or increase the likelihood of successfully developing a stem cell technology that significantly improves patient care. • The ultimate product may have less impact due to competitor products with less opportunity for random insertion, which is of current interest and concern for patients with SCD. • Combining previously successful approaches may represent an incremental improvement but does not guarantee impact. There is little pre-clinical experimental data presented in the proposal comparing the other approaches to this approach in a head-to-head fashion in animal models. • Considering the advanced genetics employed for production of the therapeutic recombinant LV used in the in vivo model, the proposed LV-based HSC therapeutic product has a high likelihood to advance understanding of globin-chain levels that are tolerable. It is not clear how improved expression would improve patient care in regard to cell health over a duration of time beyond the in vivo model. • The in vitro and in vivo functional demonstration of the bifunctional lentiviral-based therapeutic does show some significance in the research setting, but the proposed product has a low likelihood to have an impact for an unmet medical need in the treatment of sickle cell disease. • Multiple similar projects are underway in other institutions. It is not clear that this application would dramatically change the treatment landscape. • There is a lot of competition in this field, including CRISPR approaches.
GWG Votes	**Is the rationale sound?**
Yes: 7	• The data presented support the rationale for the product.
No: 6	• The data are supportive of further development of the product's assays. The data presented represent an expected compilation of supporting evidence for a product at this

	stage of development. Having already compiled process history for generation of the drug substances, many concerns are likely derisked greatly to allow for efficient translation into later stages of development. The project would benefit from further assay development to characterize the half-life of the transgene-expressed beta-globin chain in situ with the other regulated cis globin chains. ● The proposed therapeutic vector demonstrated comparable colony formation potential to other vectors, which indicates suitable vector and transgene delivery to the target CD34+ tissue. Development is recommended for further characterization of the proposed clinical construct around the impacts to viability/morphology of target cells/tissues post-colony differentiation when compared to single-functional therapeutic vectors. ● While there is theoretical merit in the combination of two different methods to make a synergistic product, this combination may not be clinically needed. In fact, studies that the two investigators are already leading with the individual components of this combined approach have yielded positive results on their own. ● The two-pronged approach may increase the risk of beta globin chain imbalance, which might make it counter-productive based on the recent data presented by Mark Walters at the American Society of Hematology 2023 meeting. ● It is uncertain that a dual construct is safe based on the in vivo data provided. Assay(s) to evaluate globin chain stability are needed to support the construct's safety and efficacy. ● The potential improvement with the two-pronged approach is not clear. The approach might be detrimental by virtue of causing a deleterious chain imbalance. ● The potential increase in potency due to overexpression using the dual construct approach may make this product more toxic. ● The advanced molecular approach to prevent sickling combined with the reduced amounts of rLV to establish a suitable copy per cell is a commendable approach. But modern criteria for what may constitute a safe and efficacious treatment for sickle cell disease is challenging to some construct-based approaches. These criteria for clinical benefit have evolved as properties emerged from the clinical setting for SCD trials over the past few years.
GWG Votes	**Is the project well planned and designed?**
Yes: 12	● The project design covers the requirements for development of an HSC ex vivo LV-mediated therapeutic product with the project's inclusion of appropriate resources and established practices to support development through the next stages of clinical activities. ● The program's design includes suitable assays and process, with process history along all stages of the proposed development. Overall this program is well designed for tangible development of a therapeutic for SCD. ● The applicants have already compiled process history for generation of the drug substances, so many concerns are likely derisked to allow for efficient translation into later stages of development. ● The reduction in timeline until pre-IND (from 30 months to 18 months) will give the applicants a better chance of being competitive in the field. ● From an operational perspective, the planning appears to be appropriate. ● The project is well designed and planned.
No: 1	*none*
GWG Votes	**Is the project feasible?**
Yes: 10	● The revised application with the removal of the extra mouse model experiments streamlines the product development. ● The outline of the project details sufficient resources within the team and facilities to complete the proposed activities appropriately. Qualifications include a team with a history of successful development of ex vivo cell and gene therapy products across many indications, including other hemoglobinopathies. ● An experienced team will carry out the project. ● Pre-clinical experimental efficacy over existing strategies shows a small effect, and may indicate that this product is unlikely to translate to a large clinically significant effect in patients. This tempers enthusiasm for the development of this product. The value proposition for the development of this product needs to be balanced based on other products that are in clinical development. ● Contingencies against the risk of oncogenic events include redesign of the construct to include insulators. However, a prior study using homologous insulators revealed concerns, and the insulators were subsequently removed from the therapy (Cavazzana-

	Calvo M, "Transfusion independence and HMGA2 activation after gene therapy of human β-thalassaemia." Nature. 2010 Sep 16;467(7313):318-22). • The proposal's contingency plan lacks details on how they would approach safely formatting insulators in a non-homologus fashion that wouldn't interfere with reverse transcription of the packaged transcript. Further resources would be needed to support potential use of insulators to demonstrate safety and suitability; ideally performed in a SCD tissue setting where the oncogenic risk may present differently than other hematological disorders. The applications should refer to "An experimental system for the evaluation of retroviral vector design to diminish the risk for proto-oncogene activation." Blood. 2008 Feb 15;111(4):1866-75. by Ryu B, et al., which may provide some direction for exploring activation concerns.
No: 3	• It is unclear whether the product will be able to complete the necessary clinical trials or be commercially viable in the number of years that it will take for marketing approval.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 9	• The applicants highlight greater unmet need in some underserved populations. • The DEI plan is well thought out and thorough. • The design of the program does present overarching applicability to provide a product which would account for the influence of race, ethnicity, sex and gender diversity. The proposal specifically notes they "have the resources and connections to be able to select a diverse group of participants. Our goal is to select persons from populations for our clinical trials that have been disproportionately affected by SCD and health care disparities" and this demonstrates some of the proposal's mechanisms to account for the respective influences. • The applicant incorporates experiences from the population that will benefit from the proposed product. With internal support from the community outreach team within their institution, they aim to focus on patients with sickle cell disease across southern California.
No: 4	*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	1	• The application includes strong data. The applicants are part of an institution with a very strong DEI track record in the clinic.
6-8: Responsive	2	• The applicant adequately presents some of the known information about Sickle Cell Disease (SCD): the demographics, disparities in the population, and how trial participants will benefit from the proposed product. • An appreciation of study bias is reflected in the application's goal to include sex as a factor in mouse model studies. • Given the availability of perspectives from advocacy groups representing adult patients and families regarding SCD, this application would have been strengthened if the aforementioned would have been asked for input.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-14692
Title (as written by the applicant)	Mature iPSC-Derived β Cell Spheroids for Treating Induced Type I Diabetes
Translational Candidate (as written by the applicant)	iPSC-Derived β Cell Spheroids
Area of Impact (as written by the applicant)	The proposed iPSC-derived, autologous beta cell product will provide a fresh and powerful treatment to pancreatomy and other type 1 diabetes patients.
Mechanism of Action (as written by the applicant)	The proposed mechanism is based on transplantation of autologous iPSCs derived Aiβ-spheroids for type 3c diabetic patients that have gone through pancreatectomy. Autologous derived iPSCs based therapies provide several advantages such as avoiding any gene editing requirements or long-term need for immunosuppressants. The Aiβ-spheroids can secret insulin in response to glucose stimulation within the first 24 hours of implantation. The beneficial effects can last for extended time.
Unmet Medical Need (as written by the applicant)	Diabetes is one of the major health challenges of the world. It is a chronic disease which requires patients to go through lifelong monitoring and therapy with no cure. It is evident that diabetes is becoming an epidemic which affects people universally that urges for new and improved therapies.
Project Objective (as written by the applicant)	Pre-IDE meeting with FDA and package for IND
Major Proposed Activities (as written by the applicant)	• Chemistry, Manufacturing, and Controls (CMC) Activities • IND-Enabling Animal Studies • Clinical Study Protocol Development, PI and CRO Identification, Regulatory Communications
Statement of Benefit to California (as written by the applicant)	Diabetes is a chronic disease that affects ~ 2 million Californians and well over 30 million Americans. Though current therapies have significantly reduced the severity of the disease, a cure still remains elusive and anti-diabetes drugs need to be administered for life. These treatments have been associated with significant reduction of quality of life. If the studies proposed here translate to cell therapeutics through clinical trials, a cure is envisioned that would help many Californians.
Funds Requested	$5,400,000
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	70
Median	70
Standard Deviation	8
Highest	85
Lowest	50
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	1
(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: 12	• The project is targeted to treat Diabetes Type 3c for the treatment of patients following total pancreatectomy. The rationale to inject/infuse iPSC-derived mature β-cell spheroids (AiB spheroids) would be a significant advancement in the clinical treatment of this disorder and could be highly impactful based on a poorly managed and in some cases unmet clinical need. • The initial plan is focused on Type 3c diabetes (referred to as induced Type 1 in the project title). However, the development of a high quality source of beta-cells that potentially could be delivered without need for immunosuppression to overcome histoincompatibility potentially would have enormous impact on the treatment of essentially all forms of diabetes, especially Type 1. • Better control of diabetes is a significant public health goal. A product such as this that can provide long term control would be significant. However, it is not clear that the program is practical given the standard of care. It may be important for those individuals with inadequate control of their glucose levels with the current standard of care. Children may be one potential population that could benefit. • The applicants do not allude to the number of subjects that have pancreatectomies but rather describe the much larger Type 1 and Type 2 diabetes populations. Of the subjects that do have pancreatectomies, some receive autologous islet cell transplants derived at the time their own pancreas is removed. • Given that others (notably Vertex) are developing allogeneic islet like transplants from pluripotent stem cells for Type 1 and some insulin requiring Type 2 diabetics, there may not be a need to develop an autologous product for those undergoing a pancreatectomy. • The project team purports to be able to generate pancreatic beta-cells from human iPS cells with extraordinary speed and efficiency using RNA reprogramming methods. • The team already has generated iPS cells under GMP conditions in a way that could set a standard for the entire field of regenerative medicine.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 4	• The idea of implanting pancreatic islets has been explored in clinical trials since the 1990s, thus demonstrating the difficulty in finding the factors that would allow for successful development of a cellular therapy. • iPSC show advanced performance in differentiation, which supports potency assays. • Conceptually the rationale appears to be strong. However, the plans to establish robust proof-of-concept, nonclinical development, and contingency plans are not well explained or well-conceived means to advance a therapy towards a clinically meaningful outcome. The clinical plan is also not well established.

No: 9	• Publications from group on RNA reprogramming to generate iPS cells go back to 2012. That part of technology seems robust and well established.
	• The data clearly show that the applicants can make iPSCs from dermal fibroblasts and bank them. For the following reasons, it is less clear whether the applicants can make a purified population of authentic beta cells which can maintain glucose homeostasis in animals or a patient.
	  ◦ Firstly, the application lacks details on the beta cell differentiation process. The applicants state that they use mRNA transfection with various mRNA cocktails to effect differentiation. No intermediate cell populations are shown or characterized. These data are critical to demonstrate proper differentiation through intermediate cell types.
	  ◦ The evidence for successful differentiation shown in Figure 1 does not describe the composition of the spheroids or the intermediate cell types.
	  ◦ The insulin staining in Figure 2a is too low-resolution to be informative. Furthermore, most cells take up insulin from high levels present in media, so staining insulin does not demonstrate that this insulin is produced by the cells. The applicants should additionally stain for C-peptide.

	● The flow cytometry in Figure 2c demonstrates a potentially problematically high proportion of Oct3/4 positive cells. The figure additionally shows 99% of cells positive for C-peptide. Those markers should not exist in the same cell if the cells are properly specified, which calls into question the validity of the differentiation approach. ● The functional data are minimal. In figure 3a, it looks like most of the implanted cells do not express insulin. ● After implantation in mice with induced diabetes, data on correction of blood glucose concentrations is shown for one mouse only. Many other groups have shown that when human islets (or their in vitro equivalents) are transplanted into rodents, blood glucose levels drop to 70-90mg/dL, which is equivalent to the human set point. Data for the one mouse included in this application show a drop in blood glucose levels that is more reflective of the mouse glucose set point. This suggests regeneration of mouse endogenous islet cells (which is a well known consequence in this particular model of diabetes) rather than glucose control from the transplanted cells. ● In figure 6e, islet spheroids and an encapsulated islet spheroid do bring blood glucose levels down to the human set point in the same mouse model. However, for two days before toxin treatment/diabetes induction (and before treatment with the islet spheroids) this mouse already had blood glucose levels in the human range. Collectively, these data make it difficult to assess the therapeutic potential of this product. ● The quality of data presented in the application could be improved significantly. On the surface, the applicants' claim to generate iPS cells extremely efficiently and then generate ~99% beta cells in about 3 weeks using RNA programming is truly extraordinary. The best supporting data may be the flow cytometry results, showing 99% of cells expressing C-peptide after differentiation. (Insulin staining alone can sometimes reflect uptake of exogenous insulin by cells, so C-peptide is crucial). However, the quality of the photomicrographs presented to document the differentiation process is poor. It seems possible from the OCT4 flow cytometry data presented that there are residual stem cells in the product. The data on reversal of a diabetic phenotype in vivo is unconvincing, as the data may be from individual mice in various figure panels, and statistics analysis is lacking. ● Publications are lacking on group's work on reprogramming and differentiation of iPS cells to beta cells, and details in patent applications do not seem publicly available at this time. This brings up a concern that some of the claims in this application are not supported by data, in light of findings of many other strong labs in the field. While others have achieved differentiation of mature, functional beta cells from iPS cells, it only has succeeded after much struggle and can't be achieved with the speed claimed in this application. The application should contain a much more complete supporting data package to be compelling. ● The preliminary data suggest that this applicants have developed a rapid, efficient method to generate beta-cell spheroids in which >98% of the cells are positive for insulin and C-peptide. If verified, this would be extraordinary and would support development of the product. However, it would be important to know that comparable results can be obtained reproducibly with iPS cells from many individuals to support the development of a product for autologous cell therapy. Applicants do not provide information on how many different iPS lines have been studied for differentiation to beta cells. ● The high percentage of OCT4 positive cells may indicate a greater potential for tumorigenicity compared to other iPSC-derived cells in development. ● It is unclear if the final product configuration has been defined. ● Based on the unclear rationale to develop a GLP lab, the applicants may not have a full understanding of the scope of this endeavor. ● The clinical rationale for testing the therapeutic approach in Type 3c diabetes as proof of concept, to avoid the problems of autoimmune rejection intrinsic to Type 1 diabetes, is sound. However, it is not articulated clearly enough. A plan for ultimately transitioning to individualized treatment for Type 1 diabetes, and taking into account the risk of autoimmune attack on newly transplanted beta-cell spheroids, is not presented clearly. ● Autoimmune destruction of the transplanted cells is inadequately addressed.
GWG Votes	**Is the project well planned and designed?**
Yes: 3	● The plan has the needed elements for successful execution. ● Project plans include product development in a dedicated GMP environment.

No: 10	• The applicants have demonstrated that they can can derive dermal fibroblasts, make iPSCs, bank them and test the banks. Additional expertise is needed for other elements of this project to inform appropriate project design. • The applicants should avail themselves of FDA input via an INTERACT meeting. FDA is not taking a lot of INTERACT meetings, so if that is not possible, an experienced regulatory consultant should be engaged. At a minimum the applicants need to consider tumorigenicity studies. • The proof-of-concept data in diabetes models was not well-executed or complete, so it is unclear whether the implantation of AiB spheroids is feasible. The overall plan to work towards a pre-IND is not clear; there is no risk mitigation plan should the intended approach fail. • The applicants' flow data shows about 6% Oct4 positive cells. The application does not discuss the intended cell dose, but it is likely more than 100 million and might be up to a billion. As such, the applicants will need to show that 6% of this dose, transplanted as pluripotent stem cells, does not cause a tumor in animals. • One thing the applicants intend to do is run their own GLP studies. This is not advisable, and the applicants should avail themselves of one of many excellent CROs that specialize in these studies. • The preclinical studies are not well thought through; the numbers may be too small to support the claims. • The final product is not well defined. Applicants present one figure (possibly from a single mouse) suggesting that stromal vasculature fraction (containing mesenchymal stromal cells) accelerates engraftment of functional beta cells generated from iPS cells. It is not clear how this will be incorporated into the final product in time for pre-IND meeting. • The suggestion of using collagen encapsulation to deliver the product isn't developed clearly. • There is no clear plan for how the applicants will work with the rare population of individuals who become diabetic after surgical removal of pancreas because of extreme pain from acute or chronic pancreatitis, although this is the primary group they plan to use to test the beta cell product. • The plan for ultimately transitioning to individualized treatment for type 1 diabetes, and taking into account the risk of autoimmune attack on newly transplanted beta-cell spheroids, is not presented clearly. • Timeline is ambitious, as applicants suggest they will be nearly ready for IND (not just pre-IND) by completion of the grant period. That displays "commensurate urgency" but seems unrealistic. • The application largely ignores years of work of multiple groups on delivery of islets and beta cells to patients with Type 1 diabetes.
GWG Votes	**Is the project feasible?**
Yes: 6	• The project is potentially feasible but is very early stage and robust nonclinical and clinical plans need to be developed with specific attention to detail and adherence to timelines. • One concern is the use of autologous iPSCs which will mean the program will need to explore the impact of different donors on the quality characteristics of the final drug products.
No: 7	• The applicants are qualified to make iPSCs and bank them in a GMP environment. Beyond that, help either from consultants or new hires would enhance the feasibility of this project. • The team is staffed with scientists who have apparently been very successful in working with iPS cells and their differentiation. They have partnered with a CRO that has a good track record for GMP cell production. They also have partnered with a stem cell company that has experience with clinical translation. However, there is a conspicuous need to add team member(s) with greater experience in pancreatic biology and in clinical aspects of diabetes. The application lacks clarity and sophistication in several areas that reflect this lack of experience, including: choice of animal models; history and state of islet transplantation; the autoimmune aspect of Type 1 diabetes; cell encapsulation including issues such as fouling of capsules, degree of protection from autoimmune attack and vascularization; design of clinical studies. • Overall, the project plan to produce GMP-grade beta-cell spheroids seems reasonable. However, the level of detail in the application is not sufficient to be certain that all essential steps are covered. Partnering with organizations experienced in GMP

	production of cell and gene therapies suggests that this can be accomplished, but crucial details still must be presented. ● GMP production of 3 iPS lines seems feasible. The plans downstream from that are not clear. The applicants do not indicate whether they will focus on autologous or allogeneic transplantation initially. If autologous, then it is not clear how they will be able to generate enough different product batches under GMP for a reasonably sized clinical trial. If they will start with allogeneic transplant, this plan is not clearly presented. ● It is not clear that the applicants have a working relationship with clinics that carry out the removal of pancreas followed by restoration of autologous islets in Type 3c diabetes. This will be essential for the proposed proof of concept clinical study. Even if the production of beta cells under GMP is robust, the team may not be in a position for a meaningful pre-IND meeting without a clear clinical plan.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 8	*none*
No: 5	● Efforts to uphold DEI principles are not clearly explained, although it is well known that some under-represented groups have a greater incidence of diabetes and suffer more adverse outcomes of their disease. ● The application merely glosses over DEI issues with some high level discussion of demographics of diabetes. No concrete plan on how subjects for first or subsequent studies might be chosen. There is inadequate information on the demographic distribution of iPS lines in their bank. ● There was not enough emphasis on this topic. ● There is so little written in these sections that it was difficult to evaluate.

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	The application includes good demographic data. Additional consideration related to how DEI could be factored into research approach should be added.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN3-14646
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 adoptive cell therapy treatment of brain cancer
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 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: 65

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

Mean	67
Median	65
Standard Deviation	9
Highest	85
Lowest	50
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	1
(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: 4	• Successful imaging would be helpful in development of cell therapies for solid tumors. • Some reviewers pointed out that the device would be utilized primarily for research purposes, not clinical decision-making. I feel that this is still important in assessing new stem cell therapies. • MPI has the potential to be routinely used as a clinical imaging modality. • Tracking CAR-T cells may not have any impact in the clinics.
No: 9	• Potentially useful for CAR T development, but not for actual clinical follow-up of patients treated with FDA-approved therapy. • I an unclear on the unmet need for this device. Tracking CAR T cells can be helpful but I doubt that the MPI machines have the resolution needed at which such images would be impactful. Moreover, the activity of CAR T cells depends on a lot of other factors than just homing to the target site. This worries me about the eventual clinical application of such a technology. The thing that this technology would help with is to show when CAR T cells have not traveled to the target site and the therapy was likely going to fail. • I doubt that this technology will be clinically useful, but may have an impact in the research field. • I would encourage the investigators to think of applications beyond CAR T cells and to propose those plans in future submissions. • Unclear as to value proposition for a clinical application. • Potential to propose a value proposition for clinical applications. • Clinical protocol may not have direct clinical application. • Unclear that tracking will be useful in routine practice for CAR T cells.
GWG Votes	**Is the rationale sound?**
Yes: 4	• This is a new and potentially exciting area of stem cell research. • The rationale for making a clinical prototype of MPI is valid. However, using it as a tool for CAR T cell therapy is not valid. The PI failed to mention the necessary FDA approval of the labeling agent and the labeled cells.
No: 9	• Interesting technology to answer preclinical questions to understand the mechanism of action. • Unlikely to have sufficient resolution or robustness to see CAR T used to treat hematopoietic tumors. • The rationale appears to be sound for the application, but the eventual clinical application seems rather far-fetched. I am not convinced that the application will be robust enough to make the type of clinical decisions investigators are hoping to make. • CAR T cells are targeted for hematological indications currently. Solid tumors are under study. Not clear if the product will interfere with functionality. Are there other potential applications for this technology? • No mention of the drug product, a critical component for imaging.
GWG Votes	**Is the project well planned and designed?**
Yes: 4	• The device proposed might allow investigators to track whether the administered stem cells arrive at the target area.
No: 9	• Good tool for lead candidate selection. • The plan for the clinical application of this product is limited. Even if successful, this product will have limited clinical application and the road to getting it FDA approved will be long. • The team should reconsider the regulatory requirements for approval. • Project has multiple components and needs focus to generate content for IND enabling activities. • Investigations of the labeled cells need to be elaborated. Instead of tagged cells, PI should use an equivalent amount (label in administered cells) of free labeling agent to see the effect in case the dead cells release the labeling agent after accumulating in the tumors.

	• The number of different CAR T cells to be tested should be elucidated. It is not clear to me that the product would act the same across the different CAR T therapies. • Frozen labeled cells may not live.
GWG Votes	**Is the project feasible?**
Yes: 7	• Making MPI as tool is feasible. • The labeling agent itself is not cleared/approved by the FDA, and so even with successful development of the device, the technology could not currently be clinically used.
No: 6	• It is difficult to assess the feasibility until the agent and its potential effect on the cells is understood. • I don't think that the team has thoroughly discussed and mitigated all the risks. Applicants are encouraged to think of applications beyond CAR T cells.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 6	• Committee felt some effort had been made regarding DEI, but could be improved. • It's challenging to assign DEI principles for a device.
No: 7	• Insufficient evaluation. • No clear plan provided. • Lacks plan with focus on DEI. • Not sure DEI principles can be assessed as rigorously with device applications as product applications.

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: 5.0

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	1	• Great partner with another California institution.
3-5: Not fully responsive	3	• Not enough explanation on DEI methods. • Building relationships with clinicians that work with patients directly and engage patient organizations to include the perspectives of the diverse voices of patients who will benefit from the device. • One of the their investors is a leading LGBTQIA+/Allies investment syndicate. The applicant has signed on as part of their network, which encourages non-discrimination and diversity policies and offers support for DEI training.
0-2: Not responsive	0	*none*

Application #	TRAN1-14629
Title (as written by the applicant)	Neurogenic hydrogel stimulation of stem cells to regenerate radiation-damaged salivary glands
Translational Candidate (as written by the applicant)	Ceviginate is a neuromimetic encapsulated in a hydrogel
Area of Impact (as written by the applicant)	Dry mouth as a result of injury to the salivary glands by radiation therapy for head and neck cancer
Mechanism of Action (as written by the applicant)	Regenerate damaged salivary gland tissue through neurogenic stimulation of stem cells
Unmet Medical Need (as written by the applicant)	Current treatment options for dry mouth/xerostomia, such as oral pills and rinses, merely alleviate symptoms but fail to address the underlying cause of dry mouth. With no regenerative treatments available, this medical condition is irreversible.
Project Objective (as written by the applicant)	pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Safety and dosing study in a large animal model • Production of R&D grade Ceviginate, development and validation of quality controls/analytical protocols, and packaging stability testing, aging • Develop First in Human (FIH) clinical trial design
Statement of Benefit to California (as written by the applicant)	Our mission is to overcome xerostomia or dry mouth through restoring salivary gland function. With no regenerative treatments available, xerostomia is irreversible. Based on this unmet need, we are developing a long-term therapeutic treatment to restore salivary flow through activating salivary gland regeneration. This will be the first regenerative treatment for this medical condition and gives cancer survivors and their families the chance to restore their quality of life.
Funds Requested	$2,384,806
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: 65

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

Mean	63
Median	65
Standard Deviation	6
Highest	70
Lowest	50
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: 9	• The proposed product has the opportunity to significantly impact not only oral health but also provide long-term benefit for patients' quality of life. • The potential for regeneration of salivary stem cells would provide a restorative benefit over current symptomatic treatments. • Patients would be less burdened with the need to constantly hydrate and experience less adverse effects known to be associated with drugs that help promote salivary secretion. • There are currently no approved regenerative therapies for xerostomia. • The goal of the proposed project is to overcome radiation-induced salivary gland dysfunction and resulting xerostomia through neurogenic stimulation of salivary gland stem cells. There are currently no regenerative treatments for xerostomia and its downstream problems, so the proposal address an unmet need. It is however unclear if the treatment is superior to currently available methods for controlling symptoms.
No: 3	• Although the proposed approach is innovative, the application lacks data to support that it will improve quality of life for patients. • The approach has the potential to be impactful, however there are no data provided to indicate how long this therapy could potentially last following treatment. Therefore, it is unclear at this time if this treatment would prove to be better than the current standard of care. • The product is proposed to stimulate stem cell-mediated actions, but no data are provided to demonstrate this. • The significance and potential for impact are unclear based on the current data.
GWG Votes	**Is the rationale sound?**
Yes: 6	• The active ingredient, cevimeline, has been commercially available and used orally in xerostomia patients. This supports the proposed clinical rationale. • Yes, the rationale is supported by rodent studies as well a clinical studies using oral delivery of the active ingredient. • Local delivery of the drug to the target organ via intraglandular route of administration, in addition to the improved formulation, is logical for maximizing salivary gland distribution and persistence. • The rationale is supported by findings by the applicant that cholinergic nerves and synthetic neuromimetics maintain salivary stem cells and promote the replenishment of healthy and radiation-damaged secretory tissue through activation of muscarinic receptors. • The ex vivo and in vivo studies conducted to date support the clinical rationale. • There is not a clear motivation for the incorporation of hydrogels. • The rationale is sound but more data are needed on the efficacy of this product • The preclinical study included in the application may not adequately replicate the disease model.
No: 6	• Yes, the project is based on sound preliminary science. • Additional data related to efficacy are needed. • The data in the application did not demonstrate improvement over the current standard of care. • The application did not address the commercial feasibility of this product. • The durability of this therapy is unclear, which leads to concerns related to translatability if indefinite repeated injections are needed.
GWG Votes	**Is the project well planned and designed?**
Yes: 1	*none*
No: 11	• The project plan is quite aggressive from a CMC perspective. While the individual components (API and excipient) are available, no work has been completed with the proposed CMO. The manufacturing processes have not been established and QC release testing that will be required has not been initiated. • Yes, however the relationship with the CMO needs to be further developed. A more detailed CMC plan would be available once the relationship with the CMO is established and therefore flushed out. It is highly likely that additional time will be needed for generating a GMP manufacturing and testing plan of the final drug product, which is lacking in the current proposal.

	• There is a risk that the project will run into delays in initial manufacturing steps.
	• There are multiple problems with the design of proposed preclinical studies:
	  • The costly 9-month study in large animals that is not GLP compliant and is not using product manufactured under GMP is not supported.
	  • A preliminary non-GLP repeat dose small animal safety pharmacology study is proposed to inform the proposed large animal safety pharmacology study. Of note, these studies are more correctly termed toxicology studies with safety pharmacology endpoints. Safety pharmacology endpoints are not required in two species, so the small animal study is out of scope of the proposal.
	  • The design of the small animal study is much larger than would be needed for a pilot non-GLP dose range finding study (both in the number of animals and scope). If the intent is to have this study serve as a second species to support safety for the IND, the study would need to be GLP compliant.
	  • The large animal dosing study would not need to be conducted to support a preIND meeting. Study design should be conducted as a GLP study following FDA concurrence of design.
	  • It is unclear whether the same design as used for small animals is proposed for the large animal safety study in this application.
	• The characterization criteria for the product is lacking. It is not clear if there is patient variability that will affect the efficacy of the product.
	• It is unclear which test article is being used for non-GLP studies. It will be important that sufficient characterization is being conducted to show comparability with cGMP clinical product.
	• No specific quality oversight program was described.
	• The proposed regulatory pathway may be appropriate but should be confirmed.
	• Given the early stage of this milestone-driven project, it is premature to initiate such large non-GLP studies without formal communication with the FDA.
	• The justification of high dose is not consistent with current agency guidance. There is also not a good discussion of dose rationale.
	• The rationale to support the proposed once a month regimen for two months is lacking and is not consistent with the currently envisioned optimal proposed clinical regimen of one dose every three months.
	• The application does not indicate a clear understanding of dosing.

GWG Votes	**Is the project feasible?**
Yes: 5	• The milestones should be achievable. • The project is feasible, provided that manufacturing is successful. • It seems likely that this proposal is feasible, but additional studies are needed to support potential efficacy. • The team would benefit from a named preclinical consultant. • The studies are feasible in animals. The team should engage consultants for an analysis of patient acceptability. • The proposal contains a risk assessment and a contingency plan but these are not detailed.
No: 7	• The application suggests poor understanding of CMC activities and the steps required to execute on a CMC plan. • CMC activities to support the product profile are lacking. The team had not identified support staff to serve as the point of contact for CMC activities. • It is unclear which internal team members will be managing all of the external CMC partnerships. • The requirements for the individual components (API and excipient) appear to be available, however the partnership with the CMO is not firm. • The timeline is quite aggressive for CMC, with no room for delays. • The aggressive timelines are concerning.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 11	• The application reflects a genuine sensitivity to DEI issues, and a commitment to making their treatment accessible to all. • The DEI information is adequate for the state of the program today. Additional information will be needed for clinical proposals. • The applicant argues that the proposed therapy will be relatively simple to administered by a physician. The applicant has also considered cost/reimbursement which will presumably allow better access to diverse populations. • Yes, the focus now is on radiation-induced damage but this approach can also be applied to other conditions.

No: 1	• The target population was not engaged in the development of this product.

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: 7.0

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	• The application includes good demographic data and assessments of research elements that take into consideration factors that may broaden understanding related to diversity.
6-8: Responsive	3	• The applicant states that there isn't data regarding the impact of this disease on various ethnic groups, noting that the literature from prior studies is silent on the topic. ◦ Because the literature related to previous clinical trials is silent on issues of diversity, the applicant intends to use the clinical stage efforts related to this product's development to better understand the incidence and prevalence among underserved populations. • The applicant reflects a commitment to DEI and intends to use the clinical stage to better understand the distribution among ethnic groups and underserved populations. • Animal models included both male and female mice. • The applicant reflects a commitment to DEI training for the team and will rely on their institution to facilitate training. • Engagement of the target population as part of the planning for this application is not reflected.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN3-14626
Title (as written by the applicant)	Optimizing Cell Therapy: Developing a Novel Delivery Device Designed to Improve Cell Therapy Efficacy
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 QMS, design control, DHF, 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	$497,063
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	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: 2	• The project strives to address a challenge that cell therapies face when infusing cells.
No: 11	• Clinical indication not sufficiently clear. • Indication is not well defined so difficult to assess impact. • Injection using a syringe might be the case for some cell therapies but many others are implanted in different ways other than a straight injection - such as loaded into a pre-existing device, delivered as organoids or clumps of cells or implanted using specialized devices in specific anatomical sites. • I agree that there is some relationship between viability and efficacy of most cell therapies as they are usually dependent on some in vivo function carried out by the delivered cells. However, whether the current hit on viability is due to the delivery device is still not clearly supported. • This application is a resubmission. The applicants were only partially responsive to reviewers comments from the first submission. The applicants need to address all the issues raised previously. • There is one piece of biological data in this application and the significance is unclear based on that data. In that data the survival they show using the prototype device is already approaching the survival of cells that have not been through any device. It is unclear whether the additional improvements they are trying to make will have significant impact. • There is not enough data in the application to assess the impact of the device. Endpoints are not well described, and may not correlate with cell viability. • The premise that shear forces on the proposed stem cell type may reduce their efficacy in liver or kidney disease is not justified by data of the PI or the literature; The proposed stem cell type responds very differently to different forces - the link to shear forces and decreased cell efficacy in liver or kidney disease was not substantiated.
GWG Votes	**Is the rationale sound?**
Yes: 1	• Improving stem cell viability is a well known goal of administering stem cell treatments (see Marquardt et al. quoted previously).

No: 12	• Many of the concerns from the previous review remain unaddressed.
	• While the applicants have improved the description of the one experiment they have I still have questions - some of which were asked on review of the previous submission.
	• Haven't defined or provided data to measure impact on cell function in a meaningful way.
	• The rationale is based on a few references in the literature and one single experiment.
	• Just looking at the one piece of data with stem cells - the cells were lifted off plastic with trypsin. That in itself is quite hard on the cells. When they are replated (without going through any device) what is the survival rate? For example, if 1 million cells is harvested when they are replated how many survive?
	  ◦ How long after lifting off the plate are cells put through the delivery devices?
	  ◦ How are the cells maintained after lifting off the plate and while being put through the delivery device?
	  ◦ What medium were the cells maintained in?
	• In the previous iteration of this grant cells were examined at days 1, 3 and 7 post infusion. Where is that data? What are the cells infused into?
	• One cytokine is measured as an indication of functionality. How long after re-plating was this cytokine measured? Were any other cytokines measured? Looking at just one cytokine at one time point is not a robust measurement of functionality.
	• There is not a clear understanding of potential differences of the proposed stem cell type with other cell types.
	• Although this is indeed published and cited in the resubmission (reference 6), it is difficult to imagine that 14% loss of viability "completely negates the therapeutic effect". As this is a key rationale driving development of the device, the group ought to produce in-house data corroborating the marked sensitivity of the cells to relatively small differences in viability. It seems more likely that other aspects of the cells which are not

	captured by trypan blue exclusion are important and altered by the freeze-thaw. In this regard, it is also disappointing that in vivo experiments to determine the impact have not been done and are not planned. Indeed, given the central argument about viability and functionality, even the in vitro measurement of trypan blue exclusion and cytokine production seems too limited. Multiple orthogonal approaches/readouts would provide greater confidence in any results. ● Other references cited in response to critiques also do not address the delivery mode as being a major problem. ● Reference 46 cited in the response is a study that actually does not test viability per se. There is no mention of any of the typical methods for assessing viability including trypan blue, PI, or 7-AAD. Instead, the authors report other measures of the cells in good vs. bad responders such as ultrastructure of cells, duration of passage in vitro, phenotypic marker expression by flow, and phosphatase activity after induction of osteogenesis in vitro. Thus, this is not really a supportive reference. ● Reference 41 is also cited in the response about rationale for increasing viability. In post-hoc analysis they found great variability of stem cells post-thaw and some suggestion (albeit not strong) that this correlated with markers of efficacy. This argues that method improvements related to freeze/thaw could be more impactful than methods focused on infusion. The infusion device is unlikely to impact poor viability due to suboptimal freeze/thaw. ● The final reference supporting their argument is not very rigorous – in a Letter to the Editor authors provide a brief narrative (without data) centered on a technical questionnaire they used to try to assess reasons for efficacy failure of an stem cells in a phase 3 study. Among several reasons, they mention "high injection speeds, causing cell death due to friction with the needle walls" as a potential problem. A number of other reasons include variables in pre-delivery phases including handling of cell vials, freeze/thaw issues, and cell resuspension. It is more of an authors' opinion as there is no supportive data. ● The target of liver and kidney disease is ambitious and each are very different. ● It is not clear if the PI plans to deliver to acute kidney injury or chronic renal disease on dialysis or at a low glomerular filtration rate to save them from dialysis. Data that support the proposed stem cell type can reverse renal failure, chronic renal disease, acute kidney failure are not included. ● There are identical concerns for liver disease. Is this targeting acute liver disease, chronic liver disease? These are different pathologies and likely require different cell numbers, densities, activation states, vesicles for efficacy. Did not see data supporting this stem cell type can cure liver disease or preliminary data showing there is signal in liver disease and now the proposal will improve the signal. ● Plan is not well developed.
GWG Votes	**Is the project well planned and designed?**
Yes: 0	*none*
No: 13	● There is insufficient information to assess the success of the proposed plan. ● The overall plan has multiple components which makes delivering on expectations concerning. ● My major question comes down to what additional improvements do they believe they need to make to outperform their prototype device and what is the justification for that? ● Only partially responsive to original critique. ● There is no context provided for the target goals for proposed success criteria for proposed experiments. ● No plans to study impact on cell function in a relevant animal model. ● It is not clear what is being done for 1.5 years with no animal work. An animal model is critical to understand what occurs in vivo in an iterative way. ● Milestone 1 should have already been performed prior to asking for funding. There seems to be very little preliminary data supporting this proposal. ● Figure 5 shows viability of the stem cells and other cell types after injection using off-the-shelf vs. their device and functionality (defined solely by cytokine production after additional culture). ● Past reviewers asked about the relevance of this particular cytokine and whether others were measured. These points are not addressed well or at all. This cytokine was measured since controlling inflammation through this pathways is one of the primary function of many stem cell therapies. However,

	this cytokine can be inflammatory – perhaps lower cytokine actually denotes a better phenotype? No data or comment on other cytokines are presented. ● It is still unclear what these cells were infused/injected into. ● Importantly, this figure shows 100% viability and IL-6 production of MSCs compared to control (cells handled similarly but not infused through a device). Thus, based on these metrics, and the group's intended focus on MSCs ("Additional testing with non-stem cells has also been completed and is shown in the graph but not discussed as part of this grant"), it is not clear what optimization is needed? Error bars indicate greater than 95% viability with the current prototype. ● All experiments are done with cells at 1x10^6 cells/ml but this is likely much lower than what is expected to be used in practice (Kabat M, Stem Cells Transl Med. 2020; PMID 31804767). There is no plan to test different concentrations/doses. ● The one cytokine tested is not sufficient to gauge stem cell function. Metabolite production and gene expression following permutations in the syringe device design are needed. Need additional expertise on the behavior of stem cells, their genomic and metabolic profiles under shear stress, without shear stress, using different cell densities, different oxygenation levels in the device, production of vesicles in the device, etc - all of these affect stem cell efficacy but are not considered here for this device. Further, these outcomes should track to the therapeutic benefit on the condition they are trying to solve with the device. ● The device is not a one size fits all. Some applications may need substantively more than 1 x 10^6 cells/ml. In the clinic, it is not uncommon to give 5-20 x 10^6 per kg in a small transfusion bag. Cell numbers affect shear force and other forces within the syringe but this is not considered; level of oxygenation with cell numbers within the device also impacts viability but this is also not considered; freeze/thaw also affects viability - most clinical infusions are given post thaw and the fragility of the membranes are very different than those cultured freshly but this is also not considered. ● The optimization plan is still rather vaguely stated. for example, what does refinement and optimization of the prototype pressure chamber entail? How is cell adhesion measured? ● In the Project Plan, goals of >20% reduction in peak pressure and shear stress and >30% reduction in cell-material adherence are stated. No rationale is provided for these goals. Why do they not prefer functional benchmarks instead (viability/function)? However, these may already be optimal with the current prototype. ● No justification is provided for a 20% reduction in shear force as an important target. How was this number decided upon? There is no data shown that justify this choice. ● The activities proposed in milestone 3 to test efficacy are not delineated with clear objectives or experimental plans; it is not clear what is being undertaken here. ● The coating objective is not well defined: what type of coating is being tested, is there a dose response curve, a maximally tolerated dose, how much leaches into the cells, is it toxic to humans or to cells? A pharmacologist with such experience could be helpful. ● Endpoints are not well defined, and the coating proposed is completely uncharacterized.
GWG Votes	**Is the project feasible?**
Yes: 5	● I believe the project is feasible. More preliminary data is essential, as well as a better explanation of the one piece of biological data that is shown in the grant and justification of why they need to improve on what they already have. ● Partially feasible.
No: 8	● Without connecting to criteria that are important to the proposed stem cell viability and function, outcomes they are working from are not meaningful. ● It is feasible to execute the program, but the data collected may not substantiate the efficacy of the device. ● Such a device may be feasible, but there is insufficient information to assess feasibility. ● Clear outcomes are not well defined so project does not seem feasible. ● The risks and mitigation strategies section needs mitigation strategies. The proposal only presents potential risks and reasons why they are unlikely to occur. Thus, the application needs thoughtful assessment of the weak points addressed with concrete plans of remedies/alternative approaches.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 10	● Multiple efforts at outreach in terms of recruiting staff. ● Appears adequate.

	• It is hard to tell from the application. This is an engineering project to develop a device to use to deliver a subset of cell therapies. Presumably the applicants would not be the ones delivering the cell therapies so I am not sure how they directly address diversity.
No: 3	• The information provided was not specific to judge the DEI principles. DEI principles were addressed for staffing. • No clinical approach.

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: 6.5

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	• The development of this particular device and the hope for improved cell viability coupled with the proposed cell treatment could allow more of the population to receive treatment for unmet medical needs.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*