APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	DEI SCORE (MEDIAN)	DEI Low	DEI High	Resubmission	Previous CIRM Funding	Disease Indication	Product Type
TRAN1-15227	Development of a Gene Therapy for the Treatment of Arginase Deficiency - Translating from Proof of Concept to Support Pre-IND Meeting	**$5,266,504**	**Y**	**95**	93	3	85	97	15	0	**8**	8	8	Y	N	Arginase deficiency	Gene therapy
TRAN1-15257	Adenine Base Editing for Autologous Hematopoietic Stem Cell Gene Therapy of CD3δ SCID	**$5,966,928**	**Y**	**92**	92	4	80	98	14	1	**9**	7	9	Y	N	SCID	Cell and gene therapy
TRAN1-15230	Ex Vivo Modified Hematopoietic Stem Cells to Treat Danon Disease	**$5,180,389**	**Y**	**90**	92	3	88	95	15	0	**9**	8	9	N	Y	Danon disease	Cell and gene therapy
TRAN1-15252	Hematopoietic Stem Cell Gene Editing for X-linked Agammaglobulinemia (XLA)	**$4,822,284**	**Y**	**90**	91	3	90	98	15	0	**8**	7	8	N	Y	X-linked Agammaglobulinemia	Cell and gene therapy
TRAN4-15222	T-Pure: Peripheral Blood Processing Tool for Point of Care CAR-T Manufacturing	**$1,302,837**	**Y**	**88**	87	3	80	90	13	1	**8**	8	8	N	N	N/A	Manufacturing tool
TRAN4-15298	Development of a low-cost, clinical-grade iPS maintenance medium for enabling stem cell therapy manufacturing	**$999,848**	**Y**	**87**	85	4	75	88	12	3	**6**	6	7	Y	N	N/A	Manufacturing tool
TRAN1-15317	Noncoding RNA drug TY1 as a therapeutic candidate for scleroderma and systemic sclerosis	**$2,590,224**	**Y**	**86**	87	2	85	92	14	0	**7**	7	8	N	Y	Scleroderma/Systemic sclerosis	Genetic therapy
TRAN1-15330	Neurogenic hydrogel stimulation of stem cells to regenerate radiation-damaged salivary glands	**$2,312,021**	**Y**	**86**	86	6	70	92	11	3	**7**	6	7	Y	N	Radiation damage	Small molecule drug
TRAN4-15253	Generation of human universal donor iPS cells	**$999,989**	**Y**	**85**	83	7	60	87	10	4	**6**	2	7	N	N	N/A	Cell therapy
TRAN1-15325	Development of an AAV gene therapy immunotherapy for the treatment of glioblastoma	**$3,997,919**	**Y**	**85**	81	8	65	89	7	7	**8**	8	9	N	N	Glioblastoma	Gene therapy
TRAN1-15341	Optogenetic Therapy for Treatment of Geographic Atrophy	**$3,998,930**	**N**	**84**	84	2	80	90	1	13	**8**	7	8	N	N		
TRAN1-15291	Pro-regenerative infusible ECM biomaterial for treating acute myocardial infarction	**$4,624,192**	**N**	**83**	83	4	70	88	5	10	**8**	8	8	N	Y		
TRAN1-15209	Clinical Development of Extracellular Vesicle-based Therapy for Alport Syndrome	**$5,166,326**	**N**	**80**	80	7	65	85	7*	8	**7**	7	7	N	N		
TRAN1-15346	A targeted antisense oligonucleotide therapeutic strategy for Timothy syndrome	**$6,112,230**	**N**	**80**	80	4	70	85	2	13	**8**	7	8	N	N		
TRAN3-15331	Spinal subpial injection system for delivery of gene-based therapies in humans.	**$2,606,723**	**N**	**80**	79	2	75	80	0	15	**6**	6	8	Y	N		
TRAN1-15239	Autologous anti-PSMA CAR-T cell controllable by focused ultrasound (FUS-PSMACAR-T cells)	**$4,449,448**	**N**	**80**	77	5	65	82	0	15	**8**	6	8	N	N		

TRAN1-15279	A novel gene therapy for the treatment of familial partial lipodystrophy disease type 2 (FPLD2)	**$4,000,000**	**N**	**80**	77	4	70	80	0	14	**9**	7	9	N	N		
TRAN1-15213	In situ vaccination with chemokine genes CXCL9 and CXCL10-engineered dendritic cells for non-small cell lung cancer	**$6,300,700**	**N**	**75**	77	4	70	86	1	14	**9**	8	9	N	N		
TRAN1-15336	Effect of Inflammatory Secretome on Epidermal Progenitor Cells	**$1,945,600**	**N**	**75**	74	4	70	84	0	15	**6**	6	6	N	N		
TRAN4-15342	Modular Robotics cluster for the automation of cell therapy manufacturing	**$1,349,069**	**N**	**75**	74	5	60	80	0	15	**8**	8	8	N	N		
TRAN1-15273	Development of a gene-modified, hiPSC-derived NK cell therapy for improved potency and durability of response in lung cancer	**$3,999,792**	**N**	**75**	73	7	65	85	1	13	**7**	7	9	Y	N		
TRAN3-15223	Development of an endovascular bioartificial pancreas (eBAP) device for the treatment of type 1 diabetes	**$1,961,058**	**N**	**75**	73	2	70	75	0	15	**7**	7	7	N	N		
TRAN1-15240	Development of Cargocyte expressing IL-12 for the treatment of Metastatic Cancers	**$3,183,602**	**N**	**75**	72	4	60	75	0	15	**7**	7	7	N	N		
TRAN4-15225	Purification of Human Hematopoietic Stem Cells (HSCs) for Clinical Stem Cell Transplantation	**$1,504,551**	**N**	**65**	68	7	60	83	0	15	**8**	8	8	N	N		
TRAN1-15264	CDC42 Inhibitors for the Treatment of Melanoma	**$2,719,482**	**N**	**60**	58	4	50	60	0	15	**6**	6	6	N	N		

* Qualify for Minority Report

Application #	TRAN1-15227
Title (as written by the applicant)	Development of a Gene Therapy for the Treatment of Arginase Deficiency - Translating from Proof of Concept to Support 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 new therapy for Arginase Deficiency, where present day this is minimally effective at best.
Mechanism of Action (as written by the applicant)	The proposed clinical candidate is a virus that has been altered to carry the gene for & produce the arginase protein in the liver of those with arginase deficiency to effectively treat this condition. It will be delivered intravenously & target the liver. Successfully restoring arginase expression in the liver will resolve the elevated arginine levels and resolve the abnormal arginine metabolite guanidino compounds shown to result in abnormal function of neurons & function of oligodendrocytes.
Unmet Medical Need (as written by the applicant)	Arginase Deficiency results in progressive cognitive decline, often with seizures, loss of milestones & frequently with children becoming wheelchair-bound. Therapy today is all dietary which is minimally effective. This proposal is to bring to an IND an effective gene-based approach as new therapy.
Project Objective (as written by the applicant)	Pre-IND meeting, then clinical trial planning.
Major Proposed Activities (as written by the applicant)	• Generate & characterize clinical-grade adeno-associated viral vectors for expressing ARG1 in liver. • Characterize safety profile of intended clinical product by a toxicology study w/clinical-scale lot. • Develop and prepare all associated documents for a 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, meaning 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 for endpoint outcomes. Our efforts will support identification and inclusion of California families in the pursuit of a therapy.
Funds Requested	$5,266,504
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	93
Median	95
Standard Deviation	3
Highest	97
Lowest	85
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	15
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/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	• Arginase deficiency (AD), a distal urea cycle disorder, is a rare and deadly enzyme deficiency disorder that requires treatment via enzyme replacement in the liver. This is best conducted by gene therapy, and the goal of this proposal is to bring a gene therapy forward through the pre-IND stage of development within 2 1/2 years. • AD is a disease that presents later in life than other urea cycle disorders, but still begins in late infancy. This disease presents with microcephaly, spasticity, seizures, loss of ambulation, growth retardation, periodic episodes of hyper-ammonemia and failure to thrive. The disorder is devastating and the presently available dietary therapies are not very effective. • The project was designed to use an virus platform to treat arginase deficiency, a rare but deadly disorder. The target is clearly defined and therefore has a high potential to impact affected patients. • With current standard of care for treating arginase deficiency oriented towards risk-adverse approaches towards disease symptoms, the proposed product is likely to provide an impact to an unmet medical need. • Yes. The proposed product is intended to provide a sustained reduction and maintenance of a therapeutically relevant (normal) target plasma arginine level to prevent disease progression. • This deadly urea cycle disease without therapeutics is an unmet medical need, especially for pediatric patients and their parents and health care professionals. • Clear unmet clinical need. Devastating disease without treatment. • Gene therapy is the only therapeutic option due to the diversity of mutations and complexity of disease. If successful, this application will be a game changer for patients with Arginase deficiency. • Considering the proposed route of administration, the delivered therapeutic gene, and the target tissue for the therapy, the tech has the potential to improve patient care with some significance. • If this research were successful, then this would change the paradigm by which AD patients are treated by moving them away from solely dietary approach (which has little benefit) to a potential curative approach. • The proposed restoration of arginase levels could potentially be curative for this patient population. • The progression from the development of the vector of choice, the generation of data needed for meetings with the FDA and the forward thinking for a pre-IND meeting are all excellent. Thus, this would be impactful and highly practical proposition for patients who currently are without effective options. • The data provided supports the programs next steps in clinical development. Both in vitro and in vivo data demonstrate potential therapeutic efficacy with a generally safe drug product profile suitable for translation into the clinic. • One drawback is that a major part of the budget focuses on personnel costs and this might limit the production of necessary data for an IND application.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• The application focuses on developing a clinical trial aiming to treat arginase deficiency using gene therapy. For that, the applicant aims to use a virus based vector to express arginase in hepatocytes of the liver. The proposal is based on convincing preliminary data showing that the gene therapy developed by the applicants can work in animal models for arginase deficiency. The data are convincing and demonstrate the readiness of this project for clinical trial. • The rationale for this approach is very strong, and at this stage the use of the proposed vectors for gene therapy is well established. • The data from animal models support the rationale as the animal models are predictive of human responses. • The data presented indicated a high potential for success in the clinical population.

	• The data provided supports the program's next steps in clinical development. Both in vitro and in vivo data demonstrate potential therapeutic efficacy with a generally safe drug product profile suitable for translation into the clinic. • The applicant has been strongly responsive to comments from previous reviewers, leading to what appears to be a greatly improved application with good attention to multiple tasks required to make this a high quality program with a high likelihood of success. • The group is using a mouse model that biochemically replicates the human disorder. Preliminary data indicate that the approach developed by this group is capable of treating AD in arginase deficient mice. They have found that mice need only about 10% of the normal levels of the missing arginase protein to result in long term survival. Treatment results in mice that are behaviorally normal and indistinguishable from litter mates, except for size. • The preclinical survival data are excellent, with 90% survival of mice out to over 6 months, as compared with death of control animals in the first month. • They have shown a sensitivity of oligodendrocyte progenitor cells to the guanadino compounds that are elevated in this disorder, and have shown that the gene therapy treatment rescues myelination in vivo. • Brain function and behavior are restored to normal levels and motor cortex pyramidal neuron intrinsic excitability is also rescued through the gene therapy approach. Benefits are also seen at the ultra structural level and in respect to dendritic arborization. • They found that gene therapy eliminates toxic levels of guanidino compounds in vivo. It also appears to restore normal arginine metabolism in the hepatocytes. • In addition to preclinical data provided with the mouse model, the proposed dosing strategy is informed by clinical data from a similar disorder which is consistent with other gene therapy indications. • Ongoing clinical trials of gene therapy for metabolic diseases in the literature are also supportive. • Virus-based approaches for gene therapy for metabolic disorders of the liver are in clinical trials for phenylketonuria and for methylmalonic acidemia. Thus, the transition to clinical trials for this general approach is well established. As in these other trials, this group is also trying to restore enzyme expression in the liver in order to resolve the metabolic imbalances associated with this disease, and their current evidence indicates that establishing expression in the liver is efficacious. • The rationale for the approach is scientifically sound. There is some minor concern around the product's potential therapeutic reach in other tissues, specifically in regard to the tissue specific vector/promoter for compartmentalized tissue expression.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 13	• The proposal is well organized, include convincing data and address key comments from the previous review. The rationale is convincing. The timeline is ambitious but feasible. • The project is very well planned and builds on extensive experience by multiple groups in trying to treat metabolic disorders of the liver using gene therapy approaches. • The program, and product design, are well constructed. Including the support of external experts in product development, the application provides the assurances of a quality setting. • The construction of this project and the development of appropriate vectors is meticulous and is pursued in partnership with first rate colleagues. • There has been excellent and extensive preclinical work on an appropriate mouse model and also on the development of an effective gene therapy approach. • As shown by the compelling and comprehensive preliminary data, this is a carefully designed project. • The objectives appear appropriate and the timeline achievable. • Timelines within the project plan do demonstrate an overall feasible expectation that is in line with CIRM's mission. With a Pre-IND planned for year 3, the year after generating clinical materials, the project appropriately focuses and dedicates time to characterize the product in vivo for efficacy. • Updates provided for the project, such as the product development and regulatory activities, appropriately plan to deliver on expectations for robust meaningful outcomes. • The applicants have also made a real effort to address the previous reviewer comments especially around the lack of expertise in clinical development for gene therapy. • The applicant has carefully addressed the key concerns in the previous review. • The CMC and nonclinical aspects were well-received. The only potential issue was the non-GLP toxicology plan which was considered surplus to requirements at this stage.

	Instead the applicants should be more considerate of the use of animals and money to conduct a single GLP toxicology study instead of non-GLP, then GLP. • There is a concern with oversight of the totality of the program. • As there are several consultants some with overlapping expertise - it will be important to clearly define roles and responsibilities. • The budget for project management appears to be extremely inflated for this stage of product development. More importantly, this program is not complex enough to warrant this excessive cost/oversight. Please revise management plan to be more commensurate for the scope of this project. • The budget for clinical planning also seems excessive for this stage of development and also due to the lack of complexity of the trial which will likely be largely benchmarked off of similar clinical trials. • The section for pilot safety is concerning considering the proposed additional support in this area. The highest dose proposed is referred to as a NOAEL which is required to be 10x the highest proposed clinical dose. It is not a requirement for a gene therapy to achieve and/or assess a 10x multiple nor is a 10x margin required to define a NOAEL. It is important that the initial clinical dose is an active dose and that the highest proposed clinical dose does not exceed a NOAEL defined by the preclinical safety study.
No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 13	• All of the proposed milestones and expected project outcomes are both logical and likely to be achieved within the proposed timeline. The application demonstrates clearly this approach is feasible. • If the project doesn't work at this stage, that would be very surprising. The attention to detail to get to this stage appears to have addressed key concerns that would represent risks. • Proposed milestones should be achievable. • Yes. Good preliminary data. Very large team of consultants and admin. • The target was clearly identified and planned program robust. • Expected outcomes are managed effectively with clear success criteria for characterization, in vivo assessments for tox safety and efficacy, patient/caregiver engagement, and regulatory planning. • Overall, the team proposed represents a strong group of subject matter experts for both product development and disease indication. The team is appropriately resourced to execute the project. • The team is well qualified and staffed. The PI laboratory has reported the seminal findings for AD and its effects on the central nervous system, and has gained extensive experience in virus- based gene therapy of several monogenic disorders over the past 20 years. In addition, they are partnering with a key person who has led CIRM-funded clinical trials in rare disorders. They are also partnering with others with excellent experience in this area. • The team bring complementary expertise. In fact, the revised application brings additional expertise which will further support the program and should help to address previous comments regarding the lack of expertise in clinical development • The resources are available for successful completion of the objectives. • Access is not limited in this proposal to conduct each aspect of the project. Aside from access to the internal systems described, the proposal includes outside consultation and scientific advisors available to facilitate the development activities planned. • Considering the standardized nature of the general product development plan, the risks presented within the proposal are sufficiently mitigated to manage any delays. • The milestones are well-defined and the timeline seems reasonable. The main limiting step could be the virus production but this aspect is managed by a professional organization with a lot of experience. So, this step should not be a problem. • In rare disorders such as this one, there is always a concern about connecting with sufficient numbers of patients but attention also has been paid to this possibility with measures in place to ensure as well as possible that this will not be a concern.
No: 0	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13	• The applicant has provided a thoughtful plan for addressing DEI principles. • Project plans include summaries of DEI principles to deliver regenerative medicine therapeutics in an equitable manner. The ultra rarity of the indication is included as an element of consideration as are the disease's general socioeconomic impacts.

	• Outcomes from the project would inform development of therapeutics with similar hepatic target tissues. Also, an unmet medical need is addressed with this therapeutic when considering underserved communities in healthcare. • This aspect is clearly addressed. Arginase deficiency is over represented in the latino population. The application have clearly identified this aspect and have access to a patient population representative of the ethnic diversity of California. • The highest prevalence for this disease is in Latino populations, followed by those with origins in Asia, African and African American populations and those with origins in Europe. • The applicant addresses populations that will benefit from the proposed product. The availability of the product when newborn screening for the indication is fully adopted will also benefit an untold community impacted by this rare disease. • There is an excellent interaction with patients and their caregivers, and other stakeholders, as well as involvement with the relevant patient organization. • The applicant has addressed the principles of DEI in considering the proposed population who will benefit from this therapy. • This was considered to be adequate.
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	0	*none*
6-8: Responsive	6	• Arginase deficiency is often cited to occur in approximately 2.8 per million live births and is described by the applicant as a "pan-ethnic" disease, with the greatest prevalence among Latinos followed by Asian and African populations, and least likely in European populations. • The gene therapy is expected to be equally effective in all racial groups and genders. • Intend to have informational sessions with caregivers/candidates who are interested and have a desire to enroll. • They expect to learn more of patient caregiver challenges and opinions about a gene therapy treatment for arginase deficiency and plan to incorporate those findings into the outreach and plan for a clinical trial. • It's clear to the investigator that the opinions of parents, patients, and other stakeholders in thoughts on the development of a gene therapy approach for arginase deficiency are paramount to its success and to meeting the needs of the families. • Good data. • Adequate DEI incorporation for proposed project.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-15257
Title (as written by the applicant)	Adenine Base Editing for Autologous Hematopoietic Stem Cell Gene Therapy of CD3-delta SCID
Translational Candidate (as written by the applicant)	The translational candidate is Autologous Hematopoietic Stem and Progenitor Cells from CD3-delta Severe Combined Immunodeficiency (SCID) Patients Corrected by Adenine Base Editing
Area of Impact (as written by the applicant)	The candidate will provide treatment for a fatal inborn error of immunity (CD3-delta SCID) affecting a genetically-isolated population.
Mechanism of Action (as written by the applicant)	Autologous hematopoietic stem and progenitor cells from CD3-delta SCID patients corrected by adenine base editing have the biological activity of hematopoietic stem cells (HSC) to achieve long-term engraftment after transplantation. The correction of the pathogenic CD3-delta mutation allows the HSC to support normal T lymphopoiesis to reverse the life-threatening SCID.
Unmet Medical Need (as written by the applicant)	By avoiding the immune complications of allogeneic hematopoietic stem cell transplantation (HSCT), autologous transplant of corrected cells should be safer: no need of a matched donor, reduced risk of treatment-related toxicity using reduced intensity conditioning, and no risk of GvHD.
Project Objective (as written by the applicant)	Pre-IND meeting for guidance on IND advance
Major Proposed Activities (as written by the applicant)	• Develop Manufacturing Plan; Produce a Clinical-Scale Lot(s) of Drug Product • Perform Additional Pharmacology and Toxicology Studies • Prepare Briefing Package and Conduct Pre-IND Meeting with the FDA
Statement of Benefit to California (as written by the applicant)	Since initiation of newborn screening for SCID in California, 1 of 65,000 births (~8/year) has been diagnosed. All SCID patients require hematopoietic stem cell transplantation (HSCT). Autologous HSCT by gene therapy may be effective and safer than allogenic HSCT. Optimization and implementation of novel methods such as base editing may extend this approach to many blood cell diseases that require HSCT in California (as Sickle Cell Disease) providing more beneficial and cost-effective therapies.
Funds Requested	$5,966,928
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: 92

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

Mean	92
Median	92
Standard Deviation	4
Highest	98
Lowest	80
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	14
(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: 14	• SCID is life-threatening and a treatment for the disease would be impactful for those individuals with the disease. The current standard of care is suboptimal with potential adverse effects such as graft versus host disease. • The aim of this project is to develop a strategy for autologous hematopoietic stem cell transplantation using a patient's own gene-corrected HSPC. This project has a high potential impact despite the low incidence of the disease, as the platform can be used for other inherited disorders. • The applicants plan to provide a therapeutic involving adenine base editing for autologous hematopoietic stem cell gene therapy of CD3-delta SCID. This is an ultra-rare disease but the platform holds significant potential for other, similar genetic disorders presenting a high value proposition. • The overall population impact of this drug product will be low, but at an individual level, base edited HSPC therapies have the potential to make a big impact in certain patient populations, particularly for those patients with inborn errors of immunity. • This project has the necessary significance and potential to have meaningful impact in the field addressing potentially an ultra rare indication. • Base edited HSPC therapies have the potential to be curative for certain disease indications such as inborn errors of immunity. • SCID is rare but severe.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• By avoiding the immune complications of allogeneic hematopoietic stem cell transplantation (HSCT), autologous transplant of corrected cells should be safer for several reasons: there is no need for a matched donor, the risk of treatment-related toxicity using reduced intensity conditioning is reduced, and there is no risk of graft versus host disease (GvHD). • As compared to using CRISPR-editing, the gene editing approach proposed here may be safer and more precisely correct the mutation because base editing circumvents the need for double strand breaks and may overcome CRISPR limitations. The applicants hypothesize that even low levels of genotypic correction (in the range of 5-10%) will generate clinical benefit. • While the actual incidence of CD3-delta SCID is low (making up ~2.5% of SCID patients), establishment of a platform like this that can be used more broadly for other inborn errors of metabolism is exciting. • Yes, the pre-clinical in vitro, in silico, and in vivo mouse studies are solid and have produced a nice body of data justifying the overall proposal and next steps. • The project received favorable responses from FDA during an INTERACT meeting due to the lethality of the disease and unmet clinical need. The applicants presented a sound nonclinical rationale which was well-received by FDA. • The rationale for ex vivo genome editing of autologous patient derived cells is solid. • Nonclinical data support the program and the FDA advice has been encouraging.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 14	• The applicant has incorporated FDA feedback to assure further successful regulatory interactions, which is one hurdle to progressing the technology in SCID and other diseases. • Yes, and the revised application addresses not only the comments and concerns of the prior GWG reviewers, but the detailed and positive counseling received from the FDA after their INTERACT meeting. • CMC and nonclinical planning is well-considered within manageable timelines. • Overall, the applicant has defined and developed meaningful pre-clinical milestones. • The authors have developed a project plan that is timely and urgent and in line with CIRM's overall mission. • The plan to execute on this project is a major strength. However, the major risk associated with successful execution of this plan is associated with potential manufacturing failure(s) which could be a complicating factor when the optimized

	manufacturing process, which is developed using healthy donor materials, are employed to manufacture the final drug product using patient-derived cellular materials.
No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 14	• The applicants provide ample prelim data and a clear plan after the INTERACT meeting. From that meeting, they received detailed and positive feedback, as well as guidance on the qualification of the critical starting reagents and drug substances, the cell processing and release testing plan, clinical trial design and the pharmacology and toxicology studies, as well as regulatory concerns which should enhance feasibility. • This project is very feasible if the applicant fully incorporates the advice they received from FDA. • The proof of concept data indicates a highly targeted effect in mice. The nonclinical testing strategy is robust and CMC readiness was feasible. • The major risk relates to the potential for not finding patient-derived material to validate the overall therapeutic strategy. The applicants have taken this into consideration and have developed meaningful contingency plans. • This is a world-class and stellar staff. • The team and the resources will support the activities.
No: 0	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 14	• The DEI section seems appropriate for this stage of development. • The applicants discuss rarity of disease but address DEI appropriately, including the ability to extend the platform to other diseases. They have a clear plan for ensuring DEI. • This was considered more than adequate considering the rare disease target population. • The application includes a strong DEI plan.
No: 0	*none*

DIVERSITY, EQUITY, AND INCLUSION (DEI)

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

DEI Score: 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	5	• The applicants' DEI plan discusses that CD3-delta SCID is most commonly found within specific populations or communities, including the Mennonites in the US and Canada and certain Japanese and Ecuadorian populations. • The patient populations to be treated will be infants and young children and as a result the applicants do not believe that there will be differences in response or treatment effect that is any different by gender. • Though there are Mennonite populations in the US and in California, especially in the Central Valley, this project will be recruiting subjects and collaborating closely with experts in Mexico and Canada. The applicants are commended for trying to make knowledge of the illness available in Spanish and Low German to the Mennonite communities in Chihuahua, Mexico. • The applicants are attempting do outreach and give assistance to parent and patient groups affected by CD3-delta SCID, especially those in Mexico and Canada. • There is adequate DEI incorporation for the proposed project. • The application includes good data on disease incidence across specific populations.

6-8: Responsive	1	*none*
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-15230
Title (as written by the applicant)	Ex Vivo Modified Hematopoietic Stem Cells to Treat Danon Disease
Translational Candidate (as written by the applicant)	The candidate is CD34+ HSPCs transduced ex vivo with a LAMP2 lentiviral vector.
Area of Impact (as written by the applicant)	Danon Disease, Lysosomal Storage Diseases, Drug Development for Rare Disease
Mechanism of Action (as written by the applicant)	Engrafted HSPC progeny will supply normal LAMP2B to the heart, liver, muscle, and brain via lysosomal cross-correction. Specifically, macrophages transfer lysosomes containing LAMP2B to cells deficient in this protein, improving autophagy and cell metabolism. This therapeutic lysosomal "cross-correction" paradigm is now well-established in the field and has already shown efficacy in lysosomal storage disorders as well as our own ongoing Phase I/II clinical study of cystinosis.
Unmet Medical Need (as written by the applicant)	Most Danon patients will either die from heart failure or require heart transplantation. No specific therapies exist for other symptoms including neurodegeneration and skeletal myopathy. Hence there is a high unmet need for new therapies for this highly morbid rare disease.
Project Objective (as written by the applicant)	Submission of Pre-IND materials
Major Proposed Activities (as written by the applicant)	• Pilot pharmacology studies of a surrogate to ameliorate DD in a mouse model of the disease. • Drug product process and assay development towards production of a clinical-scale lot of the candidate. • Pilot safety studies of the candidate.
Statement of Benefit to California (as written by the applicant)	Danon disease is a fatal disease without a cure, therefore the treatment we propose will directly benefit the citizens of California who have/will have the disease. Our findings also may assist in the development of new treatments for other rare diseases. Thus the work also has the potential to help Californians who suffer from similar conditions. This project utilizes CA scientists and laboratories. With success, it will generate additional research and employment opportunities for CA citizens.
Funds Requested	$5,180,389
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	88
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	15
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/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	• Yes, Danon disease is a lysosomal disease that causes heart failure and death by the time patients are 20-35 years old. There is not any therapeutic intervention currently. Therefore, this is a significant unmet medical need. With early enough intervention, ultimately, a single treatment would alter the course of the patient's disease progression leading to a significantly higher quality and length of life. • Danon disease is an X-Linked lethal disorder with a clear unmet clinical need for which there are no alternative treatments. • The project would be very impactful for this ultra rare genetic disease (Danon disease), because there is no available efficacious treatment. • Addresses a fatal disease with no good therapy currently. • The applicant proposes life-long durability of this product. • Strong preliminary data supports an expectation of efficacy.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• The scientific and clinical rationale is sound. • Preliminary data support further development. • The scientific rationale is supported by data, especially improvement in cardiac function and survival in the animal model. • The group has done extensive studies in a preclinical mouse knockout model of LAMP2B, a model for Danon disease. LAMP2B was detected in cardiomyocytes and neurons and this correlated with restored cardiac systolic function, improved neurocognition, and increased lifespan of the mice. They provided data supporting their hypothesis that the protein was transferred by the proposed mechanism. • The program was robust and well-considered from a CMC and nonclinical perspective. The selected mouse model was considered appropriate to establish proof-of-concept. • Cross correction is proving itself in other diseases. • One issue is whether a 6-month study is adequate to demonstrate the durability of the intervention. The investigator indicated they will ask the FDA if this is sufficient when they have their INTERACT meeting. • Exosome-mediated delivery of the protein should be considered.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 13	• This is a very well-planned program addressing major activities needed to work towards an FDA pre-IND. I had several questions that I sent to the investigator, and their responses adequately addressed all of my questions. • The plan to replace a deficient protein was well-planned and KO mouse model was considered an appropriate target. The planned studies up to 180 days to assess locomotor and neurological activity seem robust. • The project is well-designed and planned. • The objectives and timeline appear appropriate. • Good plan with long follow-up of mice. • A bit concerning that despite starting with half the number of Danon disease cells, they ended up with ~5x more cells at two weeks compared to healthy donor CD34+ cells. This is not addressed but is mitigated by being an n=1 at this point, with plans to transduce more samples including patient-derived, and looking at clonality.
No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 13	• The clinical target is clearly defined; intended milestones appear manageable. • The timeline and milestones appear to be reasonable. • The team is well-qualified to perform the work and has all necessary resources. • Team with excellent collaborators and with strong track record of similar efforts.

	• This is a highly qualified multi-disciplinary team with many years of experience doing the proposed types of studies. They have access to state-of-the-art facilities at multiple institutions. • The technology and resources are available.
No: 0	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13	• Danon disease is an X-linked disease, thus will disproportionately impact males over females. The investigators are addressing an important issue for the affected population, namely barriers to genetic testing. Implementation of more equitable screening will enable more equitable access to therapy, serving the unmet medical needs of the diverse CA population. They plan to use a community advisory board and social media to engage individuals with Danon disease to ensure diverse representation. • No issues with their plan. Good team and PI already has a cohort of patients as part of a natural history study. • The DEI section appears to be sufficient for this stage of development. • DEI was adequately addressed.
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	5	• Excellent outreach and engagement activities described. • Great DEI incorporation for proposed project. • Plan to do outreach to communities. • Will coordinate with their institution's DEI Advisors to provide trial-specific recommendations on community engagement and recruitment. • Working closely with the Danon Disease Foundation. • Strongest application this round.
6-8: Responsive	1	• Strong track record, solid data.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-15252
Title (as written by the applicant)	Hematopoietic Stem Cell Gene Editing for X-linked Agammaglobulinemia (XLA)
Translational Candidate (as written by the applicant)	Autologous CD34+ hematopoietic stem and progenitor cells (HSPC) with BTK gene insertion for treatment of X-linked agammaglobulinemia (XLA).
Area of Impact (as written by the applicant)	The candidate will provide improved outcomes for patients with XLA, by allowing autologous transplantation with reduced intensity conditioning
Mechanism of Action (as written by the applicant)	The drug product has biological activity of hematopoietic stem cells (HSC) to achieve long-term engraftment after autologous transplantation; the BTK gene insertion allows the HSC to support normal B lymphopoiesis to restore protective antibody production.
Unmet Medical Need (as written by the applicant)	Despite the life-saving improvement in health of XLA patients afforded by chronic immunoglobulin replacement therapy (IgRT) injections every 3-4 weeks, autologous HSC gene therapy could provide a one-time long-term health benefit by conferring the ability for the patient to make antigen-specific antibody responses, including IgA/IgM and relieve the need for life-long IgRT.
Project Objective (as written by the applicant)	A pre-IND meeting will be held.
Major Proposed Activities (as written by the applicant)	• Establish optimal BTK gene insertion protocol for manufacturing clinical Drug products • Demonstrate disease modifying efficacy of BTK gene insertion in XLA patient CD34+ HSPC • Prepare clinical protocol and other regulatory documents to hold a pre-IND meeting
Statement of Benefit to California (as written by the applicant)	The proposed research will lead to a curative autologous HSC gene therapy for XLA. With an estimated prevalence of 3/1,000,000, there would be ~100 people in California with X-linked agammaglobulinemia, of whom a predicted 98% would benefit from and be eligible for this treatment.
Funds Requested	$4,822,284
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	3
Highest	98
Lowest	90
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	15
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/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	• X-linked agammaglobulinemia (XLA) is an immunodeficiency syndrome that results from mutations in the X-linked Bruton's Tyrosine Kinase (BTK) gene. Males with XLA lack mature B cells and have negligible amounts of antibody production. They suffer recurrent infections (especially in the lungs) and have other inflammatory complications. • The proposed project is likely to impact an unmet medical need if successful. Patients with XLA lack mature B cells which leaves them susceptible to recurrent infections, as well as other infectious and inflammatory complications. Standard of care includes lifelong immunoglobulin replacement therapy (IRT) which is expensive, associated with high patient burden, and is not curative. Allogeneic HSCT is another treatment option and can be curative, but transplants (and required conditioning regimen) are associated with significant risks and toxicities. Thus, there exists the need for new treatment options. XLA continues to be associated with risk or infections and complications and decreased quality of life. • XLA is an inborn error of immunity. XLA patients are currently treated with life-long immunoglobulin replacement therapy (IgRT), which is expensive and does not fully protect from infectious complications. XLA can potentially be cured with allogeneic stem cell transplant, but this treatment has significant limitations including lack of normal healthy donors and potential safety issues and adverse events. There is an unmet medical need for new safe and effective therapies. • Current treatments for XLA are limited to life-long immunoglobulin replacement therapy or allogeneic HSC transplants. • Life long immunoglobulin replacement therapy is limited by the need to have a life-long therapy (monthly IV or 1-2x/week subcutaneous) treatments. Immunoglobulin replacement therapy only replaces IgG and patients continue to be at risk for infections especially mucosal infections likely related to the lack of IgA replacement. • Allogeneic HSC transplants are limited by the lack of matched donors for many individuals, the toxicities associated with the conditioning regimens, risks of GVHD and graft failure. In fact, allogeneic HSCT is generally only performed in patients with XLA that need it for an alternative reason - coincident leukemia. • The current proposal suggests developing an autologous HSC transplant approach using CD34 cells edited at a location that takes advantage of the endogenous regulation of this gene expression. The investigators propose that they could use a minimal conditioning regimen for the transplant akin to SCID. Thus, this approach would be available to all patients (autologous; this also addresses diversity) and would not have the risks associated with GvHD and myeloablative conditioning. • The applicant proposes a novel approach of autologous HSCT with gene-corrected HSC to address limitations of allogeneic HSCT (e.g., risk of GvHD). Over 100 BTK mutations have been identified, thus direct correction of specific mutation is not feasible. Thus, applicant proposes development of product with site-specific insertion of a functional BTK gene into the endogenous BTK gene locus. • The applicant is developing Hematopoietic Stem Cell Gene Editing for X-linked agammaglobulinemia (XLA) to target a rare disease indication with an unmet clinical need. The approach is to target a chromosomal translocation by gene editing. Alternative stem cell therapies have been associated with significant toxicities. • Replacing the current standard of care (intravenous immunoglobulin or stem cell transplant) with a genetic repair is impactful for patients with X-linked agammaglobulinemia. • This is a gene edited autologous hematopoietic stem and progenitor cell (HSPC) based therapy. Clinical success of this program will have an important impact on patient care. • If successful, the product will significantly reduce health care expenditures as a one-and-done treatment in contrast to the life long care currently required for XLA patients. • Yes. There is significant unmet medical need in XLA, and applicant proposes development of a compelling therapeutic approach that would address limitations of existing therapies. • More explanation on why a lentiviral approach would not be better could be provided. The PI is a world expert in lentivirus therapies, and a lentiviral approach would negate some of the concerns of double-strand breaks and translocations such as the fact that a recent case demonstrated impaired HSC engraftment following a similar approach for sickle cell disease.
No:	*none*

0	
GWG Votes	**Is the rationale sound?**
Yes: 13	• The applicants propose to use site-specific insertion of a functional BTK gene into the endogenous BTK gene locus. This approach is based on sound scientific rationale and should allow the normal BTK transgene to be expressed under transcriptional control of endogenous regulatory elements, overriding any mutation downstream in the BTK coding region. • The applicants propose to develop a gene editing approach to restore BTK activity that may provide greater safety for gene therapy than lentivirus gene modified cell therapy. • The rationale for the project is scientifically justified. Background data supports the survival advantage of BTK expressing B cells which supports the need for low level engraftment for the proposed product to be successful. This supports the need for a minimal conditioning regimen for an autologous HSC transplant akin to that used for SCID patients. • The rationale and experiments proposed is supported by published work from other groups as well as published and unpublished work for the current group including, but not limited to, demonstrating favorable outcomes in a mouse model of XLA following low level wild type engraftment, and work from the group using mouse specific DNA donor template to demonstrate low but adequate engraftment of mouse lin negative cells edited to express the human BTK gene. • The applicant proposes to use BTK gene editing using site-specific integration of a BTK cDNA for physiologic expression. Studies by the applicant have examined a number of factors affecting effective BTK gene insertion, including: comparing the on-target cleavage activity; fully characterizing the best sgRNAs for on-target and off-target activity; determining the frequency of targeted integration of a BTK homologous donor to each cleavage site in BTK; and extensive optimization of BTK gene expression cassettes. • The proposed project is based on sound scientific rationale that is appropriate for this stage of development. • The applicant has conducted promising pharmacology and pilot studies and the data justify continued development of product. • The group will now build on the above data to have a human specific product assessed in human healthy CD34 cells or CD34 cells from XLA patients and perform the appropriate toxicology and efficacy studies in vitro and in vivo in NGS mice.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 13	• The project plan is well designed and builds off of previous work, much of it funded by CIRM. There is a clear vision toward an IND application. The group has not had direct interactions with the FDA for the current application but has had multiple FDA interactions for similar projects which nicely inform the current proposal. • The program and project is well constructed and logically planned following the below steps/milestones to achieve the ultimate goal of a Pre-IND meeting and eventual clinical translation. • The applicant has nicely outlined key milestones aimed at a Pre-IND meeting by the end of this grant period. The program is well planned and led by an experienced team. The PI has been working in this field through the development of the current therapies for X-linked agammaglobulinemia. • The applicant proposed a series of preclinical studies in preparation for a Pre-IND. If studies continue to generate supportive data, there is a high likelihood that the FDA will have sufficient information to provide comprehensive feedback on IND-enabling studies and the path to IND. • The plan to use the immunodeficient mouse model for efficacy and dose-related toxicity was well-planned. • The proposed plan is rigorous. Timeline is reasonable given scope of work. • The authors are highly published on this therapy with adequate proof-of-concept. • Excellent and robust off target analyses. • The applicant will perform xenotransplant studies using the edited XLA patient cells, but more details would help for this part. XLA is rare and they only currently have cells from one XLA patient. They plan on getting cells from the collaborator (1-3 patients per year) and patients will be identified by the Immune Deficiency Foundation but it is not clear that they will obtain cells from many patients. This also may affect the goal of assessing the approach in cells from diverse patient populations. • It is unclear why they are using the selected Cas9 as it looks like there is another Cas9 that has less off-target effects (Fig 2). According to Figure 1 it also has similar BTK mini-gene integration efficiency?

No: 0	*none*
GWG Votes	**Is the project feasible?**

Yes:
13
	• The information provided support the ability to correct the defect and should result in a clinical benefit.
	• CMC and preclinical were well addressed and referred to published data in peer-reviewed journals, as well as robust preclinical efficacy and pilot safety studies planned prior to the pre-IND.
	• Yes, reasonable likelihood of being able to conduct a pre-IND meeting, though this would be somewhat data-dependent.
	• Excellent team with experience performing the proposed types of studies. They have contributed to the preliminary data. They also have experience interacting with the FDA on similar projects and will soon bring a similar project for another disease to clinical trial.
	• This group has a solid record of translating HSPC based therapies into the clinic.
	• The team is exceptionally qualified with tremendous experience in this and related areas.
	• The applicant is based at a world-class research institute that has the requisite resources and capabilities that will enable success for this program.
	• Resources and experience appear sufficient.
	• All resources are available for the proposed studies.
	• The team has taken a nice consideration of overall risks and contingency plans to minimize overall delays associated with this program.
	• The team notes the risks and they propose mitigation strategies for these risks. The top three include:
	  ◦ Reduced HSC engraftment
	  ◦ Reduced HDR efficiency
	  ◦ Off target effects and genotoxicity
	• The proposed milestones are achievable. One concern is availability of cells for XLA patients as noted above. This is mitigated by the fact that, at a minimum, they already have cells from one patient and they have efforts via collaborations to obtain cells.

No: 0	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13	• The project upholds principles of DEI and accounts for the influence of diversity on their studies. As an example they will use the CRISPR-Me database to evaluate SNPs that may increase off-target sites for their product. They also plan to screen their gRNA for toxicity/off-target effects in healthy CD34 cells from diverse populations. • The group is engaging patient advocacy groups and will incorporate perspectives and experience from the population that will benefit from the proposed product in the implementation of the project. • DEI was adequately addressed despite the limited patient population. • The principles of DEI are appropriate for this stage of development. • It is unclear, based on the application, the distribution of XLA among the different populations in California or, in fact, the world. More information here would be beneficial.
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

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	5	• Solid DEI plans, well matched with proposal.

		• Good use of indirect data to highlight/validate the disparity of patient population needs. Significant under-representation in treatment but not in incidence related to Hispanic and African American populations. • Good assessment of product development; the autologous approach avoids HLA-typing problems prevalent in different patient populations in terms of availability. • Good discussion with regards to Immune Deficiency Foundation data and interaction potential. • Good thoughts on California potential patient population, in particular related to non-white Hispanics.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN4-15222
Title (as written by the applicant)	T-Pure: Peripheral Blood Processing Tool for Point of Care CAR-T Manufacturing
Translational Candidate (as written by the applicant)	Tool kit added directly to peripheral blood allowing for purification of T cell enriched product suitable for (CAR)-T cell generation.
Area of Impact (as written by the applicant)	The goal is to generate a tool that can address one of the most expensive and rate-limiting steps in the production of genetically engineered cells
Mechanism of Action (as written by the applicant)	Our application enables translation of a novel cell selection tool that requires a simple process, peripheral blood (not patient apheresis), and a broadly available instrument platform.
Unmet Medical Need (as written by the applicant)	This potentially revolutionary approach would be a dramatic advance in simplifying CAR-T cells manufacturing, lowering cost, and thereby improving access to this life-saving therapy.
Project Objective (as written by the applicant)	Tool kit: low cost, point of care use
Major Proposed Activities (as written by the applicant)	• Produce a bi-specific binder process for cell depletion • Validate a fully closed, automated processing pathway for CAR-T manufacturing using this process • Draft and finalize SOPs for CAR-T cell manufacturing, creating the CAR-T workflow.
Statement of Benefit to California (as written by the applicant)	Access to CAR-T cells, a life-saving intervention for patients with hematologic malignancy, is hindered by high cost and limited manufacturing capacity, representing a vast unmet medical need and a significant healthcare disparity. Broad availability of CAR-T therapies, potentially in mobile units, to patients who need the therapy, is of immense value to due to the curative potential. The approach outlined will help in driving down costs all making CAR-T therapy more broadly available to all Californians.
Funds Requested	$1,302,837
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	87
Median	88
Standard Deviation	3
Highest	90
Lowest	80
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	1

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	• One of the challenges in developing cell therapy products for point-of-care use is that not all facilities, such as hospitals, have the necessary tools and resources for collecting cell materials using the standard leukapheresis technique. The proposal to develop reagents that can be used at the point of care for processing blood materials without requiring leukapheresis addresses this unmet medical need. • If successful, the proposed technique will enable the manufacturing of cell therapy products at the point of care, resulting in lower costs and time savings. Eliminating the need for leukapheresis, which often occurs at separate blood collection centers, will streamline the entire manufacturing process, from blood collection to final product formulation and patient infusion. This acceleration of the development of cell therapy products can have a significant positive impact. • If the proposed reagent for processing whole blood at the point of care is successfully developed, along with the implementation of a closed system for cell therapy product manufacturing, it will be highly valuable for both patients and healthcare providers. This innovation will provide access to low-cost products in a shorter timeframe compared to the standard industry processes currently in use. • This proposed tool project aims to address the limited availability and exceptionally high cost associated with adoptive T-cell therapies for cancer and other diseases. These therapies have demonstrated significant potential to revolutionize the treatment of leukemias, lymphomas, certain solid tumors, as well as hold promise for conditions such as HIV and other infectious diseases. However, the current patient pool benefiting from these therapies is severely constrained due to the exorbitant costs of reagents and processes, along with the necessity for specialized production facilities. The proposed product has the potential to significantly alleviate these barriers. • The current application focuses on employing a rosetting method that utilizes bifunctional antibodies to eliminate the need for apheresis when collecting T cells for genetic modification and subsequent return to patients. While this methodological approach has been validated for laboratory research (by others), it has yet to be tested for clinical product development. • The applicants' broad vision is very attractive as they aim to streamline the production of T cell-based therapies, reduce costs substantially, and enable more procedures to be carried out. Their goal is to obviate the current reliance on specialized cell production facilities, which are predominantly housed in academic medical centers and corporate entities. • The product is being developed as an innovative tool for harvesting T cells for downstream processing of a bispecific target for CD-19. The potential utility of this tool is considered to have a significant impact, especially in improving the collection of cells for CAR-T therapies. This approach differs from others and, if successful, could profoundly influence the field. While there is work to be done, it is worthwhile to advance to the next stage of development. • The overarching purpose of this Translational Stage application is to create a simplified process for manufacturing genetically modified T cells. This process aims to reduce costs and increase accessibility of these life-saving therapies. The team plans to develop a bispecific antibody that can be directly added to peripheral blood, facilitating the purification of a T cell-enriched cellular product suitable for CAR-T cell generation. Importantly, this approach eliminates the need for leukapheresis. • This project has the potential for high impact as it can significantly reduce the costs of processing cells from patients to enable their transduction with a virus to generate CAR-T cells for cancer treatments. Among the three projects I reviewed in this round, I rank this one the highest. • There are potential concerns regarding the bispecific antibody, particularly related to aggregation during production or purification stages due to the high concentrations involved. This issue might also arise during the purification steps, leading to potential loss or inactivation of the product. To address these concerns, the team should consider hiring or collaborating with experienced staff who have worked with bispecific antibody culture and purification at small to pilot scales. Additionally, there is a need for more comprehensive quality checks on the antibody, including the removal of contaminants like CHO host cell proteins, DNA, and BSA, if present in the process.
No: 1	• Although a more robust manufacturing process for cell therapies is needed, the impact of the proposed product will be limited due to regulatory agency requirements for validation.

GWG Votes	Is the rationale sound?
Yes: 12	• The scientific rationale for CAR-T cell purification appears to be logical. However, it is not clear why *[name of company]* is not developing this product, as they have had this technology for a number of years. • The use of rosetting for cell isolation to avoid apheresis is a logical approach and has been demonstrated in nonclinical bench research. The rationale for developing a closed system for cell production that does not require a specialized, dedicated facility seems sound. Similarly, the ideas to speed up cell production have a reasonable rationale. • While the scientific concept is sound and justifies the value of the proposed project, the applicant provides limited data, likely due to the early stage of product development. For example, there are no data showing the yield and purity of the bi-specific antibodies, which is essential for evaluating the manufacturability of the product. However, it is assumed that standard antibody production will be used, leading to the successful development of a cell bank and the production of antibodies with the desired quality. • The applicant did provide data on the functionality of the bi-specific antibodies using purified PBMCs spiked with a known concentration of RBCs (Fig 3) and whole blood cells (Fig 4). However, it is unclear why data for myeloid cell depletion (Fig 4) was not provided, and the rationale for presenting data for only two of the six donors used in the whole blood cell experiments (Fig 6) should be clarified. • A comparative assessment of the purity of PBMCs generated using the proposed method versus PBMCs isolated using the standard technique was not included. Such data would be valuable in supporting the quality of the proposed blood isolation technique. • The preliminary data provided by the applicant to support the feasibility of the project are based on healthy donor materials. It is not clear whether the same results can be achieved using patient blood materials. Including data from patient materials would strengthen the justification for the project and demonstrate its applicability in a clinical context. • A weakness in the proposal is that in some cases, the safety, time, and cost parameters required for successful clinical translation and broader access are not clearly outlined, raising doubts about whether they can be achieved. • There is a solid scientific rationale for reducing the scaling of T cells and enabling T cell enrichment in the downstream manufacturing process. • The potential for high impact lies in potentially removing the leukapheresis step for harvesting T cells from a regular blood draw.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 11	• From the information provided by the applicant it seems the project is appropriately planned to achieve meaningful outcomes. The information provided by the sponsor indicates that some regulatory expectations have been taken in consideration regarding the design of the project, specifically GMP considerations and the safety testing of the product. • It's important to pay attention to the potential carryover of bispecific antibodies in the process. Validation should be extended to more patient samples, particularly those with smaller blood volumes, as many patients may have anemia or lymphopenia. • The proposed technologies, including the rosetting approach for depleting non-T cells from patients' blood without apheresis, have demonstrated their basic feasibility. • However, there is a need for greater precision and clarity in defining the parameters related to performance, cost, time, safety, and quality controls that must be achieved. The current approach by the applicants appears to define milestones more as activities to be undertaken rather than specific benchmarks that must be met to progress, leading to uncertainty. • From a technical and scientific perspective, the project appears sound and presents a compelling value proposition. While it facilitates T cell product development, there is a concern that the process itself may precipitate CAR-T antibody purification issues.
No: 1	• The next submission should incorporate regulatory advice with regard to pathway to allow broad end-use. • Potential immunogenicity and impurities that may be in contact with the cell product need to be addressed.
GWG Votes	**Is the project feasible?**
Yes: 12	• The overall program appears feasible up to a certain point. It should be noted that each resulting product will need to be tested with individual investigational new drugs (INDs). • The proposed milestones generally seem achievable within the proposed timeframe. However, there is a concern that in several instances, the application lacks clarity regarding what constitutes success in achieving a particular milestone. For instance, the

	milestone related to optimizing CAR-T production using lower cost cytokine media formulations and timing does not specify the exact cost or time parameters the applicant aims to achieve. Despite these concerns, the project team is robust, experienced, and has a proven track record in developing clinical cell therapy product candidates. This experience helps mitigate the concerns about imprecise milestone definitions. ● The applicants have access to facilities for product development and a strong academic team with significant CAR-T development experience. The main caveat is that their presentation of milestones for the program could have been more clear and well-defined. ● From the information provided, It appears the team have access to resources needed to complete the proposed project. ● The proposed team appear to be appropriately qualified based on information provided. ● The contingency plan proposed by the team is reasonable.
No: 0	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12	● The proposed project plan and project design adequately addresses and accounts for the influence of race, ethnicity, sex and gender diversity. ● The applicant institution has built-in ways to access perspectives and experience from the potential patient population, and has a strong track record in upholding principles of DEI. ● Lowering cost and increasing accessibility of what is currently an extremely expensive technology would benefit the entire CA population, especially underserved minorities. ● If this tool works, it will expand access to patients who do not otherwise have access to adoptive cell therapy due to the apheresis bottleneck. ● DEI considerations in the application are suitable for this stage of development. ● DEI was adequately addressed.
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

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	7	● The applicant does a good job demonstrating that minority groups remain underrepresented among recipients of CAR-T cell therapies. The institution's catchment area is highly diverse. ● Product development is focused on developing standardized platform technologies to make new cell and gene therapies as simple and inexpensive as possible. ● The applicant states that a major goal of both the institution and their partners is to expand access to CAR-T, and other gene modified products, to locations and populations of patients who currently have no access. ● The clinic leadership, including the PI of the current proposal, is committed to embracing DEI and to championing all policies regarding DEI. ● The clinic will partner with the institutional cancer center to address the issue of inequality in cancer health outcomes across populations. ● The applicant addresses the burden of cancer on rural communities. ● The application includes a thorough discussion of the applicant's DEI enhancement strategies.

		• The proposal incorporates strong patient support. • The proposal includes adequate DEI incorporation for the proposed project. • This is a well-defined DEI plan.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN4-15298
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)	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 FGF2-G3, a novel thermostable variant 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 medium via cGMP methods for clinical application. • Evaluate cGMP-grade medium for proliferation, pluripotency, karyotype, and differentiation. • Evaluate cGMP-grade medium 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	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 87

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

Mean	85
Median	87
Standard Deviation	4
Highest	88
Lowest	75
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	12
(1-84): Not recommended for funding	3

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/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 applicants intend to make GMP quality media for iPSC expansion. This media was developed by another group and has been licensed by applicants. The medium is currently being sold as a research grade reagent and the work plan for the grant is to make GMP quality media and test it against the research grade product as well as two other commercially available media. In addition they plan to test the medium under GMP conditions. • The purported advantages of this medium is that it will be cheaper than other media that are commercially available for clinical use and that the medium will allow weekend free passaging. • The applicants claim their GMP media will be $300/L. This will be be cheaper than other GMP media of which there are quite a few (at least 7). • The applicants also claim weekend free passaging is a feature. This is achieved by using a more stable form of FGF2 and adding bicarbonate and other tweaks to help manage pH - all pluripotent stem cells use aerobic glycolysis for ATP production which produces quite a lot of lactic acid thus acidifying the medium. Growth factor depletion, acidification of the medium and glucose depletion are major reasons that pluripotent stem cells need daily feeding. • Less frequent passaging not only lessens work load particularly on weekends but also improves costs as less media is used for each expansion of iPSCs. • Having a pre-sterilized complete media for GMP cell culture would be impactful for less-expensive and more robust cell processes. • Products derived from iPSCs are expensive. The costs of iPSC expansion media are a part of that cost so if a lower cost GMP medium could be developed it would be useful. I don't think it is going to increase the likelihood of developing a stem cell technology but it could certainly decrease the cost. • The value proposition is in the decreased cost. How big an impact that has is going to be product specific. When a large number of cells is needed for a product the media cost for iPSC expansion is greater than when a small number of cells is needed as biomass is normally created at the pluripotent cell stage because of their prodigious replication potential. • This product is the lowest-cost commercially available maintenance medium for human iPS cells and has gained worldwide adoption over the last two years. Its low cost ($300 per liter) and utility for infrequent passaging make for a more affordable, low-risk option for use in cell therapy manufacturing, potentially reducing total medium costs ten-fold or more for expansion. • GMP-qualified media for expansion in culture are essential for clinical applications of pluripotent stem cells. Adding a well-accepted defined medium, and one that potentially decreases production costs, to the set available for medical applications would benefit a wide variety of patients. In this case a modest investment from CIRM is likely to bring a significant return in lowering costs and enabling clinical product developers to utilize a medium they already have utilized and prefer. • I think it's important for CIRM to support tools as well as advanced therapies, and even though it's maybe not the most exciting product, it will be helpful and provide another option. • Did a good job of addressing prior concerns and making value add clear. • One concern is whether a single medium can be useful across the broad spectrum of cells that might be grown in culture (not diversity related). Not sure whether the cost will be reduced when other reagent needs are considered.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• A research grade medium has already been developed so it should just be a matter of executing on the project to develop a GMP grade medium. • While other defined, xeno-free medium formulations are available, the one being developed by the applicants enjoys wide acceptance, has some technical advantages. Use of a stable form of FGF2 is the most significant differentiator of the product.

	• Since last submission, the 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 FGF2-G3, a novel thermostable variant that enables improved medium stability and half-life in culture. These changes will likely enable lower-cost cell culture and fewer passages, minimizing manufacturing errors and contamination risk. • I was impressed by the number of cell lines they tested. They did their homework and responded to prior CIRM reviewer comments. • The data on the research grade reagent look in line with expectations for an iPSC expansion medium. The group that initially developed the product put a great deal of effort into optimizing the medium which the applicants have licensed and their data looks compelling so I do think this medium would be useful. Having said that there are quite a number of other GMP grade media available for iPSC expansion. • One thing I find out of line with the development of a defined GMP medium for the expansion of iPSCs is the use of Matrigel for cell plating. Matrigel is an ECM complex derived from a rodent tumor cell line. If you are trying to develop a xeno-free medium for iPSC expansion then you also need to pay attention to the ECM on which you grow your cells. I asked a question about that aspect and the applicants have agreed to try some of the human defined ECMs as well as Matrigel in their studies. • The rationale to develop a research tool at the price point proposed appears compelling. One caveat is the product is largely outsourced and the applicants are relying on the creation of DMFs with some of the suppliers. The cost of developing DMFs (to the holder, is high) and this could impact the attractive pricing of the product overall as those costs are passed to the consumer (ie., the applicant). • Superficially, yes the rationale is sound. The issues may revolve around the other reagents and trace elements that might be necessary for optimal cell growth.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 12	• The program to develop the product appears to be well-constructed and the utility to include weekend-free passage was an important consideration, lowering the need and cost of media changes. • Straightforward plan with sufficient number of test cases to ensure suitability across many applications and without discrimination against any potential patient recipients of cell therapies. • The applicants intend to use third parties to develop the GMP medium and do compendial tests for sterility, endotoxin and mycoplasma. The applicants will test the medium under research conditions and compare it to research grade HiDef-B8 as well as other iPSC expansion media. They will use another third party to test the medium under GMP conditions. • Design is clear.
No: 2	• Consideration should be given to the competitive landscape. • An evaluation of the number of cell therapies that will purchase the media given every manufacturer will have specific requirements to cell optimization would be useful.
GWG Votes	**Is the project feasible?**
Yes: 13	• The program feasible with the stated objectives and resources. The company has experience with research-grade media. • All previous comments for the first submission appear to have been addressed. The product has been validated for quality. • Well-planned, feasible, also discussed comparison to other lower cost media in response to reviewer questions. • Medium already exists, and path to regulatory approval is straightforward. • The team is well versed in the technology and they are using experienced third parties to undertake most of the project. • The applicants are using experienced third parties to do a great deal of the work so I think they are likely to achieve the project within the timelines. I did suggest they follow changes in pH during extended culturing and they agreed that this was a good suggestion and will incorporate that into the plan. • I believe the team has all the resources to achieve the proposed activities. I do wonder how they are going to commercialize the medium. There are at least 7 other defined media available and most of them are marketed by multinational companies so

	they have their work cut out for them. Having said that they can always license the medium to one of these companies so I'm not too worried by that. ● The contingency plans appear adequate.
No: 1	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 14	● Media is agnostic, available to all and lower cost may increase accessibility to therapies. ● They will be testing a number of different cell lines that represent both sexes as well as different races and ethnicities. ● The medium would in all likelihood be able to grow iPSCs from any race or ethnic background (I would be very surprised if that is not the case). Beyond that I am not sure there is a lot more they could do as they are providing a clinical grade tool for third parties to use - these third parties are the ones who should be conscious of DEI. ● Some concerns were raised about whether proposed testing would ensure that the medium would be appropriate to expand cells of patients reflecting full diversity of the population. I believe that these concerns are misplaced, that the medium is "diversity agnostic", and that the proposed testing on cells of individuals of multiple ethnic groups and both sexes is entirely adequate. ● DEI appears to have been minimally but adequately addressed. ● This seems challenging for this product; I thought their efforts were reasonable. ● It is difficult to assess the DEI strengths and weaknesses for this program.
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

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	6	● Product has broad applicability. ● Adequate DEI incorporation for proposed project. ● Limited description of DEI initiatives.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-15317
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 alleviating cell stress and damage through enhancing genes that alleviate cell stress which, in turn, control inflammation and fibrosis in diseases tissue.
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)	Obtain data needed 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 an 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	$2,590,224
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: 86

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

Mean	87
Median	86
Standard Deviation	2
Highest	92
Lowest	85
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: 12	• Systemic scleroderma has a high mortality rate among rheumatologic disorders. If this product is effective at slowing disease progression, it would be game changer for the patient population. • Systemic scleroderma is an incurable disease and has a high mortality rate (~28.5%). There are no therapeutic agents that reverse the manifestations of systemic scleroderma. The applicant's submission is for an indication with significant unmet medical need. • Scleroderma is a common and severe disease. • The targeted disease, diffuse systemic sclerosis, is about as bad as the applicants describe. It has the highest mortality of all the rheumatic diseases. Currently there are really no effective treatments that substantially ameliorate the disease process. Patients with severe disease are currently treated with combination immunosuppressive therapy and at times autologous bone marrow transplantation. • The compound described in this application represents a novel class of therapy. If ultimately successful, it would certainly impact an unmet medical need. Furthermore, formulation as an oral drug would set it apart from many other agents used in systemic sclerosis. This would also likely improve recruitment and equity from a clinical trial perspective.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• The applicant has done a good job of summarizing the scientific and clinical rationale and proposing a mechanism of action for TY1 within the context of autoimmune disease. • The previous application was unclear regarding the exact mechanism of action (MoA) of TY1 within the context of SSC. In the current resubmission, the applicants provide new data supporting a specific MoA which mediates a therapeutic effect in various preclinical mouse models. • The animal models described in the nonclinical data package are the best available at this time. • The data supplied is provocative. Specifically, the use of multiple orthogonal mouse models (bleomycin and tight skin mouse) is a strength. • Regarding rationale, it makes sense to focus on the diffuse subset of systemic sclerosis, as this has the worst prognosis. There exists a precedent for RNA targeting medications in other diseases such as amyloidosis and DMD. • The applicants found that macrophages are required for TY1 efficacy and that macrophage depletion abolishes the disease modifying activity of TY1. This finding is interesting and potentially a bit concerning, given that several other cells have been very much implicated in systemic scleroderma disease pathogenesis including NK cells, B cells, and T cells.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 11	• Overall, the applicants have reasonable and well-planned milestones and timelines. The budget for this proposal looks reasonable. • The applicants do a good job describing their approach, plan, and timeline. The team appropriately leverages its in-house expertise as well as FDA and RNA consultants. One team member in particular is fully capable of crafting a phase I randomized control trial study design. • The objectives can be met within the proposed timeline. • The applicants provide good preliminary data and answered previous critiques adequately. • Overall the project plan is well designed, but the risk mitigation plan is very superficial. There are still outstanding potential risks associated with CMC and translation of the proposed drug product into the clinic. It is a good start that the applicant has hired experts and consultants, but the applicant needs to do a more comprehensive job of highlighting potential risks path to the clinic.
No: 1	*none*
GWG Votes	**Is the project feasible?**
Yes: 12	• Consultants will help guide the development. • The applicants have sufficient time to get to an IND.

	• Yes, the project is feasible. • Yes overall, though concerns remained on manufacturing. • The applicants will need regulatory support for CMC as soon as possible to translate the product and prepare for IND submission. • Yes. The applicant has done a good job of addressing previous concerns. However, the applicants may still be a bit naive with respect to the CMC, regulatory, and manufacturing requirements that will enable this project to go into the clinic. To this point, the applicants have brought on qualified personnel with prior CMC and regulatory experience that will hopefully guide the application to overall success and translation into the clinic. • No. The applicants don't seem to have completely thought through risks and delays. For example, with respect to product development, the applicants state "We do not anticipate any risk related to product development. We have accounted for batch reproducibility for the experiments described in this proposal." However, the applicants don't show any batch-to-batch reproducibility data in the application. They don't show any data in the application that justifies their lack of concern with respect to product development and batch to batch variability.
No: 0	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12	• From a DEI perspective, as the applicants point out, systemic scleroderma is a disease impacting Black patients disproportionately to other races. And, as in most autoimmune diseases, women are disproportionately impacted. As mentioned previously, the oral formulation of this compound may also enable clinical trial designs that would provide access to more rural areas/populations. In addition, it may be easier for patients lacking mobility/transportation as it is easier to administer an oral medication at home rather than have multiple infusion appointments. The applicants point out several DEI enhancement strategies including mandatory training for all institution personnel. • The DEI plan seems appropriate for this stage. • DEI is adequately addressed. • The applicant did a good job here.
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	5	• There is adequate DEI incorporation for the proposed project. • The application includes very good data on disease incidence and impact with acknowledgment of greater disease aggressiveness in blacks and higher mortality. Data are also provided on young black females and overall outcomes are reflected in the plan for development.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-15330
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)	The proposed product 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 product, 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	$2,312,021
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: 86

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

Mean	86
Median	86
Standard Deviation	6
Highest	92
Lowest	70
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	11
(1-84): Not recommended for funding	3

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/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	• This proposed product is a reformulation of a currently approved drug with a different route of administration. This product may offer the potential for improved patient outcomes. • The application does not clearly specify the number of individuals affected by this condition, and it would be beneficial to provide further clarification on the impact of the proposed product. • Radiation treatment for head and neck cancer often affects the salivary glands, leading to dry mouth (xerostomia). The current standard of care (SOC) has side effects that often result in non-compliance, or is not highly effective. The applicant has developed a combination product with the potential to regenerate endogenous saliva-producing cells and sustain them over at least the medium term. Consequently, the product addresses an unmet medical need. • This product activates endogenous stem cells, promoting the production of acinar cells and the reconnection of parasympathetic neurons, which in turn leads to at least medium-term saliva production, alleviating dry mouth. The local delivery of the product in a slow-release formulation ensures the production of saliva for at least several months, and possibly longer. • The active ingredient is already known to impact saliva production. The local delivery of this product in a sustained-release formulation reduces or eliminates potential side effects and extends its efficacy over a longer period. • The project has a high impact due to its significant value proposition for addressing an unmet clinical need. • The goal of the proposed project is to address radiation-induced salivary gland dysfunction and resulting xerostomia through neurogenic stimulation of salivary gland stem cells. Currently, there are no available therapies for radiation-induced dry mouth/xerostomia, making this project crucial for addressing an unmet need. • The product is built on the discovery that cholinergic (parasympathetic) nerves and synthetic neuromimetics help maintain salivary stem cells. Successfully developing this product could improve aspects of patient care. • Yes, the proposal is particularly promising in terms of its potential to enhance the quality of life for patients. Additionally, the potential for long-term benefits, driven by stem cell-mediated tissue regeneration, sets it apart from the current SOC.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 11	• The active ingredient in the proposed product is already known to increase saliva production and is FDA approved. • The animal model studies had positive results, and it is now appropriate to advance this product into translation. • The rationale is based on the applicant's findings that cholinergic nerves and synthetic neuromimetics maintain salivary stem cells, promoting the replenishment of healthy and radiation-damaged secretory tissue through the activation of muscarinic receptors. • Proof-of-concept studies in mice and dogs have provided evidence for efficacy and have elucidated the mechanism of action for the therapy. Some preliminary data support the notion that radiation-damaged salivary glands can be functionally regenerated through the activation of cevimeline. • The provided data support the development of the product, but remain relatively weak regarding long-term benefits of treatment. • Yes, though there is an outstanding concern around the durability of the response. • Overall yes, though the rationale for conducting extensive studies, including toxicology studies, with a non-GMP product may be questioned. • The rationale for the proposed product is sound and supported by available preclinical data.
No: 1	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 11	• The objectives appear appropriate. • The project has been well thought through and, where appropriate, the applicant has engaged consultants to guide them. • They have chosen an appropriate regulatory pathway that will limit the work they must do for FDA approval. • The applicants have permission to refer to DMFs that already exist for the active ingredient and the alginate encapsulation gel. • The CMOs are all highly qualified to execute on the program.

	• The applicant provides excellent, detailed responses to criticisms from the previous GWG review. • This is a milestone driven proposal with a clear design.

No:
1
	• There are some design problems related to preclinical evaluation of dosing.
	  • A 2-week pilot study is currently funded and underway. The results of this study should be taken into account when designing subsequent studies. Early data from this pilot study suggests that the highest dose may not be well-tolerated.
	  • The applicant states that a non-GLP study is necessary to inform a repeat-dose GLP toxicity study. The proposed clinical study design suggests a single dose, which would make a repeat-dose GLP toxicity study unnecessary.
	  • If repeat dosing is still being considered, the applicant should note that the clinical regimen won't likely involve monthly dosing via this route of administration. Preclinical data on monthly dosing are not likely to be relevant or translatable to the clinic.
	  • The proposed non-GLP study intends to use 30 animals at 3 dose levels: 5, 25, and 50 mg/kg, with a control group dosed on Day 1 and Day 29. Typically, dose-ranging studies are conducted at higher doses (in this case, 25 to 50 mg/kg) to determine a maximum tolerated dose (MTD) before conducting the GLP study.

GWG Votes	**Is the project feasible?**
Yes: 12	• The objectives and timelines appear feasible. • No major concerns were raised, and the CMC and nonclinical testing strategy appears to be feasible. • The team has been well-assembled, covering the expertise needed. • With the CMOs and regulatory consultants in place, I believe the proposed timeline is realistic • The team is well-qualified, and where necessary, they have engaged CMOs or consultants to fill any gaps. • Yes, the team has access to all the necessary resources to conduct the proposed activities. • The contingency plans have been well-developed. I don't see this project as having a high level of risk. • The proposed timeline should be feasible, and reasonable contingency plans have been provided.
No: 0	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12	• The proposal adequately integrates DEI for the stage of development. • The applicants have done a reasonable job addressing DEI in this application. This product is likely to serve diverse populations. Head and neck cancer is fairly uniformly distributed across races/ethnicities, although more men are affected than women. • All aspects of DEI appear to have been adequately addressed. • The influence of race, ethnicity, sex and gender diversity is taken into account in the proposal. • This product meets the needs of diverse populations. • DEI training of the team is conducted. • The applicant proposes DEI enhancement strategies that should improved access to underserved racial/ethnic communities.
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	5	• The proposal includes adequate DEI incorporation for the proposed project. • The applicant was unable to locate data that discusses impact based on race or sex. They state that given this lack of information, their clinical strategy will be built on the need to reflect the diversity of the California based communities. • Plans incorporate the need for access to the product for use by underserved populations. • The applicant aims to Improve access by increasing the range of health care providers that can administer treatment. • The applicant plans to disseminate information on the product and the target indication broadly. • Plans include DEI training for the team.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN4-15253
Title (as written by the applicant)	Generation of human universal donor iPSC cells
Translational Candidate (as written by the applicant)	Universal donor cell that is a genetically-engineered iPSC clone and is equipped with a safety switch.
Area of Impact (as written by the applicant)	Regenerative medicine including replacement therapies affected by immune rejection by host immune cells.
Mechanism of Action (as written by the applicant)	The universal donor cell mitigates immune rejection by host immune cells and is equipped with a suicide gene to remove the donor cells in case of an unwanted situation.
Unmet Medical Need (as written by the applicant)	Provide iPSC clones as useful tools to the iPSC community to overcome immune rejection.
Project Objective (as written by the applicant)	Generation of gene-engineered hypo-immune iPSC
Major Proposed Activities (as written by the applicant)	• Genetic engineering of our proprietary iPSC. • Characterization of genetic and safety status of the engineered iPSC clones. • Manufacturing of research-grade cell bank that will be shared with the iPSC community.
Statement of Benefit to California (as written by the applicant)	The company is building a team in California to perform the planned activities which will contribute to the state's economy. The iPSC clones generated as a result of the project will be made available to researchers in the state who have activities through CIRM and otherwise, supporting the advancement of the industry in the state.
Funds Requested	$999,989
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	83
Median	85
Standard Deviation	7
Highest	87
Lowest	60
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	10
(1-84): Not recommended for funding	4

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/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 concept of creating a universal donor cell for genetic modification to enable a wide range of cell therapies is noteworthy, although it presents limited novelty. • One of the significant obstacles in the development and commercialization of pluripotent stem cell therapies is the host's immune system, which can lead to rejection of grafts. The applicant is pursuing a strategy involving advanced gene editing technology to mutate immune recognition genes (e.g., HLAs), introduce genes that suppress the immune response, and allow for graft cell elimination if needed. The success of this strategy could have a substantial impact on pluripotent stem cell therapies. • While the approach of creating a universal donor iPSC is promising, it is essential to acknowledge the complexity of the immune system, which has multiple redundant systems. The effectiveness of the strategy proposed by the applicants remains to be seen. • This project is deemed to have high impact and significance for a variety of cell therapies. It aims to provide a universal iPSC product with limited HLA expression, allowing differentiation into various cell types without the risk of rejection or graft-versus-host disease. This approach addresses the challenges associated with finding HLA-matched donors and enhances accessibility to allogeneic cell therapies. • Although there are still challenges in developing a "universal" iPSC, the potential impact on cell and gene therapies is substantial, as it eliminates the need for donor-recipient matching. This approach could also provide one-time therapies. • The availability of universal donor cells could have a major impact on the field of cell and gene therapies, although the complexity of development may vary depending on the cell types into which the universal iPSCs are differentiated. Banks of differentiated, HLA-deficient, immune-neutral cells could greatly enhance the availability and success of various cell therapies. • The cost of therapy development using this platform is expected to be considerable, and there is no estimate provided.
No: 2	• There are major potential safety concerns with respect to the potential widespread clinical use of iPSCs lacking fundamental immune regulatory proteins (multiple HLA gene products) and which likely bear additional genetic changes introduced by extensive manipulation via CRISPR or related technologies. These safety concerns will apply to therapeutic products incorporating the manipulated cells. CIRM should not fund this application. • It's not clear what the commercial pathway is for this product.
GWG Votes	**Is the rationale sound?**
Yes: 10	• The work to date is clearly described and appears logical and well organized. Limitations are discussed and experiments have been performed to evaluate their impact. Competing approaches are described and evaluated. • The scientific rationale is well presented and the results from the experiments performed to date are clearly presented in the Investigational Studies Summary Table. These investigations form a logical sequence of events leading to the present proposal. • The applicants have demonstrated they have the ability to generate iPSCs with multiple knockouts and gene additions and end up with cells that are able to differentiate into all three germ layers as well as remain genetically stable. • The data appear convincing in that the results clearly demonstrate an effect when using the genetically-modified cells in vitro. The responses against T cell rejection, NK cytotoxicity and macrophage cytotoxicity look promising, as does the in vitro and in vivo safety switch data using rapamycin, and the karyotyping frameshift analyses. • The steps described by the applicants appear logical and progress has already been made in achieving the goals of loss of HLA antigens and downregulation of immune responses against the modified cells. • The applicant previously made an earlier generation universal donor cell with distinct modifications. Those cells underwent a battery of QC tests and were shown to have all the desired characteristics of an iPSC line with a normal karyotype and differentiation potential. A clinical grade MCB was made. While the iPSCs were susceptible to treatment with rapamycin, unfortunately the applicant found that in some differentiated cells the kill switch did not work probably due to inactivation of a promoter. The plan for this project is to generate similar iPSC lines but, with an additional kill switch under the control of a different promoter. These cells will be available for distribution to the research community. • The plan to include a new synthetic promoter that cannot be inactivated is the major strength of the technology.

	• There are likely to be a large number of remaining issues, probably related to the types of cells into which the universal iPS cells are differentiated. The proposed studies are logically presented and should help to resolve some of these questions. • The scientific rationale is sound. A survey of potential customers for user acceptance criteria would be helpful. • The data as described support development of the project.
No: 2	• The overall rationale is sound but fraught with unknown biology and safety risks associated with both the kill switch and the concept of knocking out HLAs.
GWG Votes	**Is the project well planned and designed?**
Yes: 10	• The applicant is developing a cell line with downregulated HLA gene expression and a kill switch. This approach allows other researchers to manipulate these cell lines to overcome immune rejection and offers flexibility in further genetic modifications, including the addition of exogenous genes. This is a good strategy. The addition of another Rapa kill switch is also a good idea. When a cell line is engineered to be suitable as a universal donor cell it will evade immune rejection, so you want to be able to eliminate the cells in the event something untoward happens (like further mutations leading to uncontrolled growth). • The applicants are building on their prior work, which gives them a solid foundation for this project. Their approach seems logical and feasible. Realistic timelines and the intention to distribute the resulting cell lines to other researchers can accelerate the development of universal donor cells. • The project is technically well-designed, but the regulatory strategy is unclear. The applicants possess a valuable starting material and a novel promoter that can advance the field. It's noted that there is no master file in the United States, and the technology is being developed in another country, with lab space rental planned in California. • The proposed studies are well-organized, with clearly presented tasks and associated risk and mitigation analyses. The timelines appear reasonable, although there is no indication of informal meetings with regulatory agencies in either country. Regulatory guidance could offer valuable insights into assay design and required testing. • The major outcome of the proposed studies is making candidate universal donor pluripotent cells available to other facilities and collaborating to evaluate their potential for treating specific target diseases. This collaborative strategy provides diverse perspectives and insights, potentially mitigating risks. Mention is made of quality studies, but there is no presentation of a quality program. • The senior investigators are well-qualified, and the applicant organization, a subsidiary of a company by the same name in another country, is expanding its American activities, including the opening of a California wet lab for much of the proposed work. The roles and functions of the U.S. subsidiary are not entirely clear. • The proposal mentions three scientists by name, with expertise in the project's scientific and manufacturing aspects. Although the proposal mentions collaborations with ten global partners (pharmaceutical companies and academic centers), the extent of their involvement in this proposal is not detailed. • It remains somewhat unclear who will perform the various sub-projects outlined in the proposal, except for occasional mentions of the California wet lab.
No: 2	• The proposal does not address any future interactions with the regulatory authorities. • The functionality of kill switch needs to be proven in differentiated cells.
GWG Votes	**Is the project feasible?**
Yes: 12	• The project is considered technically feasible and has a strong foundation in good preliminary data. • Feasibility is expected, given the methods have been previously employed by the group to generate the starting material, reducing the likelihood of delays. • The team is highly qualified for the work, and the potential delay in wet lab space readiness is addressed with a contingency plan to utilize contract services if needed. • The contingencies have been well thought out, enhancing project preparedness. • While the technical feasibility of generating the proposed cell lines is apparent, the biological and clinical translation into a practical and viable approach for clinical use remains uncertain. • Demonstrating the safety of these cell lines for a broad range of therapeutic products presents a significant challenge, as does overcoming regulatory hurdles and facilitating technology transfer to the United States. • The application is well-organized and logically presented. However, it lacks details about who will conduct the proposed studies and where they will be performed, which is a notable concern regarding feasibility.

	• Resource descriptions for the facilities are lacking in detail, although some information about a California contract lab is provided. There is mention of ongoing collaborations, but further information on the resources available at these sites is absent. • A detailed Risk and Mitigation Strategies section is provided, with elements outlined for each proposed sub-project, demonstrating careful consideration of potential challenges and contingencies.
No: 0	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 10	• The section on DEI needs further development, but may be appropriate for this stage of development as the final cell products and indications may be more suitable for the DEI assessment. • The DEI activities proposed were adequate for a project at this stage. The likely impact of a clinical product on accessibility to underserved racial/ethnic communities is discussed, as are strategies to address these types of issues during product development. • The concept of developing a universal donor cell for cell therapies will mean that minority groups with rare HLA types will have equal access to a cell therapy. • This is adequate, though there is little detail.
No: 2	• The DEI section did not adequately address how the technology could impact Californians.

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	5	• DEI incorporation for the proposed project is a bit lacking. • The proposed development of a safe genetically engineered universal donor iSPC would greatly advance DEI; however, the applicant has not done a very thorough job of characterizing specifics about how this might take place. • There is only one cited reference in the DEI discussion, and issues specific to California are not mentioned. • Most of the DEI plans and activities described are rather provisional. For example, the applicant proposes engaging a consultant on DEI matters, but do not mention what this consultant would help them achieve. Likewise, they say they will engage a team of scientists and workers to assist with DEI matters without any description of what that might mean. • The applicant does propose to develop a community advisory council, but do not offer no clarity about why or how. • The applicant states that relevant materials will be translated into appropriate languages without naming what languages they might need. • Finally, they reference plans to overcome the social determinants that would prevent engagement and utilization of their tools but without telling us what those negative determinants might be and for whom.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	1	• Not meaningfully responsive to DEI issues or opportunities.

Application #	TRAN1-15325
Title (as written by the applicant)	Development of an AAV gene therapy immunotherapy for the treatment of glioblastoma
Translational Candidate (as written by the applicant)	An experimental AAV gene therapy for treating glioblastoma
Area of Impact (as written by the applicant)	Cancer - solid tumors
Mechanism of Action (as written by the applicant)	Following delivery with an AAV, engineered cytokines are expressed from within the tumor to kill the tumor from the inside out, they are then further secreted to stimulate local immune cells to kill remaining tumor cells from the outside in at the tumor margin.
Unmet Medical Need (as written by the applicant)	Brain tumors are the 10th leading cause of death in the United States. Glioblastoma is the most common and deadliest brain cancer, with ~13,000 diagnoses annually in the US. The 5-year survival rate is 5%. Here, AAVs deliver cytokines with potent anti-tumor activity.
Project Objective (as written by the applicant)	Pre-IND
Major Proposed Activities (as written by the applicant)	• Rodent studies to determine Maximum Tolerated Dose and PK/PD studies • Full CMC and process development for both plasmid and viral production at GLP/GMP • Production of master cell banks for cGMP plasmids and human cells used for viral production
Statement of Benefit to California (as written by the applicant)	This TRAN1 award will support the development of a novel AAV immuno-gene therapy – SRN-101 – for treating patients with glioblastoma. Glioblastoma is the most common primary brain tumor in adults and second in children. This award has the potential to bring direly needed effective therapies to the 1,400 Californians diagnosed with glioblastoma each year. [Applicant name] headquarters and employees are based here in CA so this award will support the CA economy both directly and indirectly.
Funds Requested	$3,997,919
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	8
Highest	89
Lowest	65
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	7
(1-84): Not recommended for funding	7

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 13	• Glioblastoma remains an unmet medical need. • Glioblastoma is a major and potentially fatal disease with significant unmet medical need. • Need for novel therapies for glioblastoma is enormous. • The project is intended to treat a patient population for which there is an unmet clinical need and a vulnerable patient population. • Solid tumors, such as glioblastoma, are historically difficult to treat, and therefore the proposed product has the potential to impact a significant unmet need in this patient population. • Often glioblastomas cannot be surgically removed at all, or only in part. This treatment could offer an impactful option. • As this gene therapy has already been studied clinically, the main difference is the route of delivery. The applicants would benefit from a stronger case for why cytokine administered in this way has a potential to produce better results.
No: 0	• The applicant aims to manufacture a viral vector product for gene therapy targeting brain tumors. Brain tumors have a history of numerous clinical trial failures due to challenges related to tumor location within the brain, the delivery and distribution of therapeutic agents, and suboptimal trial design. In its current state, the proposal does not sufficiently address these challenges to inspire confidence in its potential. • The proposed product certainly addresses a life-threatening tumor type that is in desperate need of new and effective therapies. However, this disease has experienced a series of failures in late-phase clinical trials, despite promising preclinical and phase 1/2 trials. Consequently, it is imperative to apply extremely rigorous standards before advancing into the translation phase.
GWG Votes	**Is the rationale sound?**
Yes: 8	• Overall, the project's scientific rationale is based on established principles of gene therapy safety and the immunomodulatory properties of the cytokine expressed by the gene therapy. The preclinical data support the potential effectiveness of the AAV-cytokine therapy for GBM treatment. • AAV vectors are primarily non-integrative, which reduces the risks of insertional mutagenesis and potential tumorigenesis for patients. This may concur a safety benefit. • From a CMC perspective, the use of AAV has been well-established. The CMC plans are comprehensive and robust. • The project seems to have a solid foundation, but there remain concerns regarding the route of administration (ROA). Some of the material may not adequately reach the tumor site, potentially leading to issues with dosing. • There are also concerns about whether a single injection is sufficient in the dosing regimen. • It's worth mentioning that there is no neurologist on the team. A neurologist could provide valuable input to inform the Target Product Profile (TPP). • The data in Figure 5 shows a positive survival effect, but the legend is incomplete, causing confusion. Have the data been selected to emphasize the apparent survival benefit?
No: 5	• The cytokine expressed by this gene therapy product may hold potential benefits, but it's crucial to give further consideration to potential adverse effects. These effects may not manifest in animal models. • The ability to effectively target the desired site with the AAV vector when administered to humans may be limited, as animal models may not accurately represent human responses. • The applicant has not presented sufficient mechanism of action data for the drug product. The gene expressed is a pleiotropic cytokine. While Figure 2 offers a theoretical mechanism of action, there is no actual data demonstrating that their proposed drug product effectively activates microglia, NK cells, or T cells in pre-clinical models. It remains unclear whether the drug product functions as described within the context of clinically relevant disease models. • The historical use of this type of cytokine for cancer treatment and the efficacy data provided do not offer a compelling basis for the project. • The proposal includes limited preclinical data. While the overarching concept of delivering this cytokine within a brain tumor using a clinically available method appears sound, the analysis of preclinical data lacks rigor.

	• More detailed preclinical data are necessary, as the figures presented are minimal. It remains unclear, for example, whether the viral vector, known for its tropism in the central nervous system, will be expressed by brain cells, the majority of which are non-dividing.
	  • The data indicating complete eradication of the tumor (shown by H&E staining) should be strengthened through immunohistochemistry (IHC) for human cells.
	  • Additionally, some analysis of failures should be included, exploring potential reasons such as technical issues related to the injection site, vector uptake failure, or biodistribution issues.
	  • The relationship between tumor volume and the success of therapy should also be examined.
	  • The investigators may need to prioritize rat studies and provide more detailed plans for actionable steps.

GWG Votes	**Is the project well planned and designed?**
Yes: 9	• The plans appear appropriate for this stage, including the development of analytical methods and manufacturing processes. • The overall project is well-planned and designed, but the rationale lacks some key mechanism of action (MoA) and pre-clinical translational data needed to justify the drug product development. • The project seems reasonably well-planned, and the delivery device is not novel. There is a plan to establish the maximum tolerated dose (MTD). While the mouse allograft model showed a 60% reduction in size following treatment, this may not be clinically sufficient for a favorable outcome. Consideration could be given to adjusting the dosing regimen, possibly by increasing the number of injections. • The CMC plans are well-designed and should be achievable within the proposed timelines. • Multiple vendors are being evaluated for the manufacture and testing of starting materials and the final product. • Biodistribution studies are needed to understand whether the therapy will effectively influence immune cell recruitment intratumorally, the timing of delivery relative to surgery, and other relevant factors. • The manufacturing proposal is reasonable, with significant expertise in AAV9 manufacturing at scale due to its use in various clinical trials. However, clinical planning elements need improvement. Concerns related to convection enhanced delivery (CED) following resection, such as achieving adequate biodistribution, need to be addressed. The issue of dose finding is also challenging, as previous approaches have not been successful in clinical settings. • The manufacturing plan is acceptable. The proposed efficacy studies require statistical power analyses to determine the appropriate number of animals, as they currently appear to be low. • It is essential for the team to collaborate with an experienced neuro-oncologist and neurosurgeon to develop a proper clinical protocol plan during the investigational new drug (IND) preparation phase. Several considerations, including the possibility of splitting the MTD into more than one injection, need thoughtful study. • The relationship between the administration of the proposed product and standard of care (SOC) should be carefully considered, especially regarding concurrent administration with TMZ (temozolomide) during chemoradiation, as TMZ interferes with DNA replication. These issues raise concerns about the team's readiness to navigate the anticipated IND.
No: 4	• Supportive preliminary data are not adequate.
GWG Votes	**Is the project feasible?**
Yes: 11	• Consideration to the intended study designs should help to strengthen the nonclinical outcomes and target product profile (TPP). There were some concerns raised as to whether targeting INF-Beta will be sufficient overall given the heterogeneous cell type to be targeted. • The CMC plan is sound. • The timeline reflects a good balance of manufacturing and non-clinical activities. It seems well thought out and reasonable. They have a good sized in house team and appear to have selected primary and backup contractors for manufacturing.
No: 2	• The team needs neuro-oncology and neurosurgery expertise.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13	• DEI considerations appear to be adequate. • While the plan discusses outreach and training, it would be valuable to outline how DEI will be integrated into the research itself throughout the research process.

No: 0	• Access to sophisticated therapies is severely restricted in the United States, with significant disparity along socio-economic and race lines. The team does not offer creative approaches to this issue. • They discuss reaching out to foundations; they should consider reaching out to Black and Latino patient advocacy groups.

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	*none*
6-8: Responsive	5	• The proposal includes good data on the demographics of this indication. • The applicant lays out incidence rates by race/ethnicity and gender, and discusses disparities in the fatality rate (which differs considerably between insured and uninsured patients). • The company will engage with professional DEI training services so that they can interact with all patient populations more effectively and in a culturally sensitive way. • A prior version of the project plan used only female mice. In the revised approach, the applicant has added studies using a new rat model of glioblastoma to be performed in male animals, as well as a comprehensive biodistribution and safety assessment to be performed in both male and female healthy mice. • The applicant is engaging patient advocacy groups as well as primary care providers to ensure planned dosing regimen is feasible and fits into the standard of care. • The applicant states they will work closely with patient advocacy groups dedicated to brain cancers to enable broader audience reach and connection with patients, families and caregivers. • The proposal adequately incorporates DEI for the proposed project.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-15341
Title (as written by the applicant)	Optogenetic Therapy for Treatment of Geographic Atrophy
Translational Candidate (as written by the applicant)	Optogenetic gene therapy for patients with geographic atrophy age-related macular degeneration (AMD).
Area of Impact (as written by the applicant)	Blindness from geographic atrophy age-related macular degeneration (AMD)
Mechanism of Action (as written by the applicant)	Gene therapy to deliver optogenetic protein to the targeted cells of the retina to restore vision.
Unmet Medical Need (as written by the applicant)	Geographic atrophy (GA) age-related macular degeneration (AMD) is an advanced form of AMD and is a very common disease of the eye retina affecting 1-1.5 million patients in the United States. Prevalence is expected to double by 2040.
Project Objective (as written by the applicant)	Pre-IND completion.
Major Proposed Activities (as written by the applicant)	• Confirmatory studies in visual response after treatment with optogenetic protein. • Confirmed appropriate cell transduction, expression, and preliminary safety. • Process development and manufacturing of product (CMC).
Statement of Benefit to California (as written by the applicant)	Age-related macular degeneration (AMD) is a major cause of vision loss in older Americans. It is estimated that >100,000 Californians are blind from geographic atrophy (GA), one of the two advanced forms of the disease. Patients experience gradual loss of central vision resulting in loss of the ability to read, recognize facies drive and loss of independence. There are no treatments to reverse GA or restore lost vision. We are developing a potential breakthrough treatment that may restore lost vision.
Funds Requested	$3,998,930
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: 84

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

Mean	84
Median	84
Standard Deviation	2
Highest	90
Lowest	80
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	1
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 12	• Geographic atrophy (GA) is a prevalent condition with one approved therapy that may slow the rate of disease progression. Restoration of vision would be welcomed. • GA due to age-related macular degeneration (AMD) is a very common condition. • Yes, the application is focused on GA, which is an advanced form of AMD and is a very common disease of the eye/retina affecting 1-1.5 million people in the United States. • With the aging global population, prevalence is expected to significantly increase in the coming decades around the world.
No: 1	• The therapy is not targeted to the cells required to be impacted in this clinical indication.
GWG Votes	**Is the rationale sound?**
Yes: 9	• GA is caused by the progressive degeneration of the outermost layer of the retina, the retinal pigment epithelium (RPE), and underlying choroid. The applicant proposes to use optogenetics to address this disease. • The applicant has bioengineered an optogenetic protein, optimized for human vision and delivered using an adeno-associated virus (AAV) vector variant developed for low dose intravitreal delivery to the retina. • Pre-clinical data suggests that this approach has the promise to restore high resolution vision to patients with GA. • Questions were raised about the appropriateness of the model and approach for this specific disorder. Nevertheless, this candidate is worth advancing to the clinic.
No: 4	• The cell target and models selected do not directly support the program. The data collected to date may not translate to humans. • It is unclear how this technology will produce enough quality of benefit to significantly impact geographic atrophy. • The nonclinical model used was not appropriate for the AMD clinical indication. The triple-knockout model mimics photoreceptor pathology, but the target disease has a retinal pathology.
GWG Votes	**Is the project well planned and designed?**
Yes: 8	• The application is a continuation of a previous TRAN proposal. Their previous TRAN project proposed four Operational Milestones. The applicant has successfully achieve those milestones and is seeking funding to further advance their lead into the clinic. • The team has delivered on other CIRM grants and appears to have the expertise to successfully complete the objectives. • The application requires more definition of human efficacy endpoints and how the nonclinical data will support the rationale for human trials. • Although the applicant has done a great job with the overall pre-clinical and CMC package, there remain some questions regarding whether the triple knockout mouse model is actually the most effective and predictive model for GA. The applicant should explore other models, such as the SOD2 model, that may be more clinically relevant for GA and AMD.
No: 5	• The overall plan is sound. However the rodent model is not appropriate. A better model would have been the SOD2 (bestrophin) model. • Other nonclinical models, such as SOD2, would be more appropriate.
GWG Votes	**Is the project feasible?**
Yes: 13	• The timelines and objectives appear suitable for drug development provided nonclinical information can be strengthened. • The applicant has done an excellent job of proposing feasible milestones and demonstrating a track record of success for this drug product. • The applicant has done a really good job with highlighting potential risks and risk mitigation plans. • Technically yes, but the candidate would be more suitable for other forms of eye disease such as retinitis pigmentosa based on the pathological progression of vision loss. • Yes, there are good background data and good expertise. The project will likely work (in a photoreceptor deficient disease) but translation to a clinical trial (where GA is a tissue rather than a single cell disease) will be risky.
No: 0	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13	• The application advances a one-time outpatient treatment by a general ophthalmologist (who does not have to be a retina specialist) and can reach underserved and rural

	communities in California and the rest of the US that lack hospitals and large treatment centers. ● The applicant has done a great job considering demographic, socioeconomic, and geographic factors within the context of DEI. ● An evaluation of the patient demographics has been conducted. ● Yes, the applicants recognize that the target disease is mainly in older white females. ● This appears to have been well addressed. ● Yes, to the extent reasonable 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: 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	0	*none*
6-8: Responsive	6	● By making the treatment accessible to a diverse patient population, evaluations of effectiveness within racial minorities is feasible. The planned treatment regimen is enabling. ● The applicant will collaborate with data partners, using historical trial recruitment data and US census data, to develop site strategies that adequately reach a patient sample reflective of the GA population's demographic makeup. ● The attention to detail on the historical use of therapeutic modalities for AMD indicates that the applicant will work to use understanding of populations to advance the project. The intention to assess male and female animal models is a first step towards understanding gender differences in responsiveness. ● Yes, extensive work is planned to incorporate patient perspectives. ● There is adequate DEI incorporation for proposed project. ● The application includes an adequate DEI plan.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-15291
Title (as written by the applicant)	Pro-regenerative infusible ECM biomaterial for treating acute myocardial infarction
Translational Candidate (as written by the applicant)	Injectable biomaterial derived from the natural scaffolding of pig hearts
Area of Impact (as written by the applicant)	Improving the quality of life of patients with heart attacks
Mechanism of Action (as written by the applicant)	The proposed mechanism of action is through recruitment of the body's own stem cells and reducing inflammation to heal the heart.
Unmet Medical Need (as written by the applicant)	The prevalence of heart attacks is high yet there are no therapeutics that can adequately prevent heart failure.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Manufacture product to support nonclinical studies required by FDA • Nonclinical safety studies • Clinical trial planning and development
Statement of Benefit to California (as written by the applicant)	The prevalence of heart attacks in California is high in adults. The significant reduction in quality of life necessitates the development of new therapies for these patients. Our injectable biomaterial is a cost effective regenerative medicine strategy to improve cardiac function.
Funds Requested	$4,624,192
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 83

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

Mean	83
Median	83
Standard Deviation	4
Highest	88
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	5
(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: 13	• As an adjunctive therapy to primary coronary intervention after an acute myocardial infarction, the product may improve clinical outcomes for these patients. Given the large number of individuals affected, the impact on public health could be significant. • The potential for impact is high and significant. Prevention of left ventricular (LV) remodeling following acute myocardial infarction (AMI) is a significant unmet clinical need. • The new Infusible Extracellular Matrix (iECM) biomaterial will immediately treat the heart to reduce the impact of ischemia and reperfusion, thereby reducing negative LV remodeling, preventing heart failure, and significantly improving patient quality of life. • Major concerns include that the material comes from hog farms, and porcine virus testing needs to be done for each batch of material. The current extraction process is highly manual, and significant process development and optimization need to be performed to produce large-scale products. • A viable treatment for AMI to prevent progression to heart failure would have a major global impact. The investigators propose the use of an infusible extracellular matrix (iECM) protein solution to be delivered at the time of percutaneous coronary intervention (PCI) to achieve this goal. • The ability to deliver the ECM product at the time of PCI is both promising in that its effect could occur earlier and be more beneficial. However, the approach is problematic in that informed consent will have to occur within a very short (~90 min max) window under emergency conditions, a situation that is unlikely to occur. This means that it may likely require an EFIC (Exception From Informed Consent), which in turn means the product requirements for outcomes are different. The PI and team should explore this with the regulatory agency prior to moving forward. • There is potential, although the impact on stem cells and the field in general is limited. It is not clear what this particular project contributes to CIRM's focus, as the material is not particularly novel.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• This proposal is a follow-on from other investigations with similar products. Preliminary data support the further development of the product. • The applicants are leveraging information from a prior project that had a successful IND, but safety concerns related to epicardial injections and transcatheter infusion based on the vulnerable myocardial wall indicate the need for an ECM product that can be infused into the myocardium. Patient consent may be difficult to obtain prior to PCI intervention, limiting patient eligibility. • The applicant proposes the single (or repeated) infusion of an ECM solution at the time of PCI. Although the scientific rationale is sound and the preliminary data are fairly convincing, the regulatory route may require different studies than those proposed. For example, if EFIC (Exception From Informed Consent) is required, then a preclinical survival impact study may be needed. Additionally, if the product is regulated as a biologic and biodistribution studies show retention at 14 days preclinically, then the design of the acute toxicity studies may need to be altered. • An INTERACT meeting, based on the existing data and clinical use, could guide the PI in the next set of preclinical studies and might shorten the path to the clinic. • The preclinical data presented are strong and provide a solid rationale for moving to the next stage toward a pre-IND meeting. The acute studies demonstrate the potential for decreased endothelial leakage, increased angiogenesis, and recruitment of reparative cells. The animal model data further show improved cardiac performance compared to controls. • The prior safety record of a related product after injection is suggestive of safety for iECM once it is delivered into the cardiac parenchyma. Functional data demonstrating safety, including the preservation of blood flow and no occlusion via angiography or microsphere studies, would reduce concerns regarding intravascular infusion.
No: 1	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 10	• The team has extensive experience in navigating these types of products through the regulatory process, including the successful completion of the proposed objectives. • Reviewers have provided compelling reasons for the applicants to seek FDA advice prior to the funding of this application to help design the studies appropriately. • The applicants plan to conduct acute toxicity and biodistribution studies to build upon knowledge gained from their predecessor product, and conduct biocompatibility studies

	equivalent to those submitted as part of that IND. The applicants intend to conduct these studies prior to obtaining FDA feedback. ● Proof of concept (POC) studies indicate a longer biodistribution period than 14 days. The product, whether categorized as a biologic or device, will require toxicity studies that align with this biodistribution profile. CDRH is likely to consider this as a prolonged or permanent therapeutic, and therefore, it is advisable to seek advice through an INTERACT or pre-IND meeting before proceeding with additional studies to ensure alignment with the biodistribution profile. ● The mechanism of action of the product remains unclear. If the applicant opts to submit a pre-IND through CBER (as they did previously), there will be a requirement to characterize the drug substance and establish specific mechanism(s) of action. However, given that the iECM is acellular, the product may warrant device designation through CDRH, which leads to a PMA (Pre-Market Approval) rather than a BLA (Biologics License Application). The criteria for product characterization are typically less stringent for devices (PMA). ● The applicant has put together an outline of the manufacturing plan for iECM, the clinical plan and draft Phase 1 clinical protocol, and the design of definitive IND-enabling preclinical studies to support an IND and initiate human Phase 1 clinical testing of iECM hydrogel in acute MI patients. ● This research program is very thorough. The applicant will perform qualification using a broad range of existing identity and purity analytics.
No: 3	● The applicant should aim to have an INTERACT meeting or get solid advice and feedback regarding the best regulatory path for development of this product. ● This product could be categorized as a medical device, in which case the pathway would be faster and the costs of development reduced. Being regulated as a device would make a very significant impact, and therefore worth addressing with FDA. ● The studies proposed are all requisite to move ahead to a pre-IND meeting. That being said, an INTERACT meeting could address unknowns based on the unique timing and route of administration which differ from the predecessor product as indicated above. This may be especially important if the regulatory path is not as anticipated or the safety profile becomes an issue due to route of administration. ● The suggested clinical design raises two questions: 1) How will the investigators ensure recruitment of patients given the short window of ~90 minutes door to balloon time in many institutions? 2) How will recruitment of underrepresented individuals be assured given the lesser access of African-American and Latin individuals to interventional procedures? ● Why are cardiac volumes the chosen surrogate endpoint? Volumes measured by echo can be subject to multiple potential pitfalls. Seeking to reduce those or demonstrate the reproducibility of the measurement both within and across patients and temporally will be important. It will also be important to adjust these measures for age, gender and body size, which is not discussed and may increase trial size. ● The PI of this program has successfully taken other products through phase 1 studies and continues to perform top tier academic research. The planned clinical, manufacturing, and regulatory partnerships are important and assuring.
GWG Votes	**Is the project feasible?**
Yes: 10	● The PI has previous experience in taking ECM products through production, as well as preclinical and clinical studies, and is therefore familiar with the required processes. The clinical investigators are well-versed in first-in-human clinical studies. ● The PI has extensive experience with injectable biomaterials for treating myocardial infarction and leads a team of experienced researchers. ● The team comprises clinicians, a project manager, and post-doctoral researchers to execute this project. ● The applicant has a good chance of achieving their expected outcomes. ● The ease of manufacturing is a plus, and the relative cost of manufacturing should be comparatively low. Consequently, the product should be well-positioned in the market. ● The proposed plan for a pre-IND is feasible, but whether it is the right plan and whether the proposed clinical study is feasible will require input from the agency. ● The timeline appears to be adequate for completing both bench and pre-clinical studies as outlined, provided that the manufacturing of the compound occurs in a timely fashion. ● The applicant has included time buffers in their projected timeline for manufacturing, assay development, in vivo studies, biocompatibility studies and safety studies. ● It is advisable to seek regulatory input before proceeding with more nonclinical and biocompatibility studies.

	• Obtaining guidance from the agency about acceptable assays will be crucial, given the unique route of administration. The development of mechanistic assays or a potency assay is an important component of the package. • Concerns still persist regarding the logistics of administration and obtaining consent from patients. Additionally, there are concerns about the size of the materials. • There appears to be some redundancy in the preclinical surgical staff required for the studies. • The recruitment of laboratory staff may pose a challenge, but the PI has a reasonable mitigation plan to shift current staff to this project. • It appears that this product may fall under the regulatory purview of CBER as a device or HCT/P (Human Cells, Tissues, and Cellular and Tissue-Based Products). There is a concern regarding the strict requirements for the timing of administration.
No: 3	• There are concerns regarding the translatability of this approach if it needs to be administered at the time of PCI, as this would likely require planning an EFIC-based study. Meeting requirements for an EFIC study necessitates highly compelling data, particularly in terms of survival or as a surrogate measure thereof. Achieving this level of evidence will be a challenging hurdle to overcome.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13	• There is no question the team is committed to inclusivity. However, the plan to recruit patients from underrepresented communities who currently remain underrepresented in trials of this nature is complicated by the very short clinical window in which patients will be eligible to be enrolled. Overcoming DEI barriers during a very short clinical window will require extraordinary effort. At a minimum, the investigators will likely need to begin to build engagement and referral systems within the community prior to any emergent events to be successful. • The information provided in the application appears to be appropriate for this stage of development. • DEI plans are acceptable for the stage of development. • DEI was adequately addressed.
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

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	7	• The proposed project incorporates DEI well. • The applicant has a strong DEI track record. • The institution has a very strong track record related to broad-based patient access and enrollment in trials. • The process and the demographics of the catchment area support access as a product moves into clinical trials. • The proposal includes good demographic data on incidence, mortality and disparities in diagnosis and treatment. The applicant has factored these health disparities into their plans for product usage and product development. The product is enabled for broad usage, but timing of administration is essential. As such, promoting equitable diagnosis and hospital access will be key.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-15209
Title (as written by the applicant)	Clinical Development of Extracellular Vesicle-based Therapy for Alport Syndrome
Translational Candidate (as written by the applicant)	Human Amniotic Fluid Stem Cell derived Extracellular Vesicles (hAFSC-EVs) that exhibit kidney-protective properties.
Area of Impact (as written by the applicant)	Kidney diseases like Alport Syndrome with limited therapeutic options.
Mechanism of Action (as written by the applicant)	The product exhibits potent kidney-protective effects through two key mechanisms: Firstly, it acts by trapping excess Vascular Endothelial Growth Factor (VEGF), preventing harm to the glomerular cells of the kidney. Secondly, it contains specific molecules, called miR-93, which reduce VEGF expression and contribute to the recovery of kidney function.
Unmet Medical Need (as written by the applicant)	Our therapeutic candidate addresses the unmet medical need for Alport Syndrome, an orphan disease, by offering a cost-effective off-the-shelf therapy.
Project Objective (as written by the applicant)	Successful pre-IND meeting with the FDA.
Major Proposed Activities (as written by the applicant)	• Develop a scalable and GMP compatible production process and establish comprehensive quality assays. • Assess biodistribution, safety, dosing, and therapeutic efficacy of the therapeutic candidate in Alport Syndrome mice. • Prepare pre-IND briefing packing and conduct a successful pre-IND meeting with the FDA to conduct phase I clinical trial.
Statement of Benefit to California (as written by the applicant)	Our therapeutic approach offers immense benefits for California by providing a tolerable, safe, and effective alternative to costly dialysis treatments and kidney transplants for AS patients. This therapeutic potential extends to other kidney diseases, offering viable solutions to more patients and transforming California into a hub for innovative EV-based therapies, driving economic growth and advancing regenerative medicine across the nation.
Funds Requested	$5,166,326
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	7
Highest	85
Lowest	65
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	7*
(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 applicant has selected an initial indication to develop a therapy that may have broader application in chronic kidney disease (CKD). However, Alport Syndrome is a rare form of CKD with a genetic basis. This is a reasonable approach, but the applicability to broader CKD will be impacted by its wide range of causes and risk factors. • The applicant seeks to develop a therapy for Alport Syndrome, a rare, inherited disease which amongst other things is associated with CKD. If successful this treatment may impact other forms of CKD, but that is not a given. • The product comprises extracellular vesicles (EVs) derived from a clonal amniotic fluid stem cell (AFSC) line. If successful, the product could improve patient care with a stem cell derived product. • Use of EVs from mesenchymal stromal cells (in this instance AFSCs) to treat CKD associated with Alport Syndrome, is in principle an attractive concept. There is a major unmet medical need for which regenerative medicine approaches theoretically could provide a solution. • The durability of the hAFSC-EVs will be important for the therapy to have meaningful clinical impact. • The project is conceptually strong with the potential to address significant unmet clinical need. • The product has the potential to mitigate the growing burden of CKD. • The product's impact will depend on efficacy and the translation to other forms of CKD.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 9	• Inflammation and fibrosis are key contributors to the progression of CKD. EVs may be able to reduce inflammation and thus support tissue regeneration. EVs are not expected to affect fibrosis. • The best in vivo data are from a single intracardiac injection of mouse AFSCs into Alport syndrome model mice, resulting in improved kidney function and prolonged survival. In a preliminary study, injection of AFSC-derived EVs instead of cells into these mice showed improvement in proteinuria. There is a risk that the AFSC-EVs might not be as clinically effective as AFSCs, but development is still warranted because EVs would ultimately be a more practical, lower cost therapy. • The rationale appears sound, though supporting proof-of-concept data in appropriate models are limited. • The data support the rationale for the application.
No: 4	• The applicant must develop additional preliminary efficacy data for this proposal. The applicant refers to a published study of intracardiac injection of mouse AFSCs - not human AFSCs, and not EVs. They refer to a second published study using human AFSCs (not EVs), but in an injury (rather than AS) model. One preliminary study of AFSC EVs shows a decrease in proteinuria, which does not seem compelling. • Do the published data on mouse AFSC injection suggest a potentially clinically meaningful benefit? The effect appears to be marginal at best. This is in line with the limited relevance of many other mesenchymal stem cell animal models to disease modification in humans. • The applicant needs efficacy data with their proposed product (human AFSC EVs) before proceeding. • The mechanism by which AFSC EVs would act is not clearly defined. The current efficacy data provided are insufficient to warrant funding. • The preliminary data are not compelling.
GWG Votes	**Is the project well planned and designed?**
Yes: 9	• The proposed experiments are appropriate and should bring the program to a successful FDA interaction. • Challenges will include assessing quality and consistency of the product. The plan outlines various analytical methods in an attempt to characterize the EVs. Regulatory discussions on this point will be important.

	• The potency assay seems complex, but it is also early on in development, with time to refine and simplify the approach to demonstrating potency. • Their plan to track the EVs using magnetic iron oxide nanoparticles appears to be a good approach. Sensitivity will be a key question, as well as understanding the impact on the nanoparticles on the behavior of the EVs. • Biodistribution can be determined by labeling exosomes with In-111-oxine and SPECT scanning. • The applicant should consider whether the research cell bank can lead to a GMP cell bank when it is processed with fetal bovine serum.
No: 4	• From a manufacturing perspective this project seems underdeveloped. The starting MCB is a research cell bank; the applicants propose to undertake retrospective QC testing for GMP compliance. This does not sound viable. The applicant should enlist regulatory guidance. • While it might be possible to qualify the MCB, it is usually better to start again - derive a cell line in a clean room with appropriate documentation. Testing quality into a product is not normally the best route. • The efficacy data are insufficient. This project should not be funded until the applicant provides robust data showing efficacy of the final candidate (hAFSC EVs) in a relevant preclinical model. • The main shortcoming of the application is the limited data demonstrating disease modifying activity with the final candidate. A nonclinical study in, for example, the ApoL1 KO mouse model would be informative to assess the effects of the therapeutic at different dose levels.
GWG Votes	**Is the project feasible?**
Yes: 11	• The assembled team is experienced with these types of products, and the necessary resources are available to the team. • The team is qualified in the biology but need advice from CMC and CMC regulatory experts. • Possibly, but the proposed project is complex and the applicant may not achieve their goals within the TRAN timeline. • The milestones appear to be realistic.
No: 2	• The applicant needs efficacy data first.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12	• The applicant has taken DEI into consideration and has adequately addressed it. • The applicants appear cognizant of the disparities in populations most affected by the disorder, with African American women being the most vulnerable. The applicant addresses DEI effectively.
No: 1	• While the applicant notes that CKD disproportionately affects Blacks and those of Hispanic descent, they do not describe an important genetic aspect. A polymorphism in the apolipoprotein L1 (APOL1) gene substantially affects the risk and age of onset of CKD and is prevalent in the Black population in California and across the USA. • The proposal should address whether APOL1 status influences the phenotypic presentation of Alport Syndrome and the potential impact of the proposed therapeutic product. I.e., will coincidence of Alport Syndrome and the high risk APOL1 allele would be examined in the proposed studies? • This question should be built into the preclinical research, to the extent possible, and in the planning for future preclinical studies that would be considered in a pre-IND meeting.

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	6	• The applicant is aware of relevant health disparities; African Americans and Hispanics reach end stage kidney disease significantly earlier than whites, suggesting inequities in disease progression and healthcare accessibility. • The applicant's goal is to make GMP manufacturing more cost-efficient, to make their therapy accessible and affordable to all patients. • The applicant has foundation partnerships for accessing first-hand experiences, perspectives, and insights from patients and their families. • The applicant also has a consultant/partner for their comprehensive DEI initiatives, which range from workshops and training sessions on unconscious bias and cultural competency. • The applicant team's leadership has extensive background in DEI engagement. • There is a strong track record of DEI implementation at the applicant institution. • The applicant has adequately incorporated DEI into the proposed project.
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 fifteen Grants Working Group (GWG) reviewers. A supportive minority of seven reviewers unanimously scored the application ’85,’ which was the recommended score from the disease area expert who reviewed the application. Overall, the panel broadly agreed the proposal has adequate significance and potential impact (criterion 1), is feasible (criterion 4), and upholds principles of DEI (criterion 5).
The majority (eight) scored the application ‘80’ or below – six scored from ‘75’ to ’80,’ and two scored ’65.’ Reviewers in the majority indicated that the project rationale (criterion 2) and the project plan (criterion 3) were insufficient for the project to merit funding at this time, for reasons given in the Review Summary under the response 'No' for these criteria.

The supportive minority diverged from the majority in the evaluation of the strength of the project’s rationale (criterion 2). One supportive reviewer described the project as “conceptually strong;” another explained that the proposed extracellular vesicle (EV) product has the potential to reduce inflammation - one of two "key contributors to the progression of CKD" - and thus support tissue regeneration. Overall, supportive reviewers were impressed by the applicant’s published and preliminary data showing improved survival in a mouse model of Alport Syndrome following injection of a product surrogate (the relevant stem cell), in combination with reduction of proteinuria in this mouse model following injection of the final candidate (EVs derived from that stem cell). One supportive reviewer explained, “[t]here is a risk that the AFSC-EVs might not be as clinically effective as AFSCs, but development is still warranted because EVs would ultimately be a more practical, lower cost therapy."

Both majority (score < 85) and minority (score = 85) reviewers noted potential improvements to the project plan. One supportive reviewer suggested that addition of nonclinical study in the ApoL1 KO mouse model could bolster efficacy data for the final candidate. Reviewers on both sides encouraged the applicant to seek regulatory and CMC guidance.

Application #	TRAN1-15346
Title (as written by the applicant)	A targeted antisense oligonucleotide therapeutic strategy for Timothy syndrome
Translational Candidate (as written by the applicant)	Timothy syndrome (TS) is a rare, potentially fatal disorder affecting the brain and the heart and is caused by genetic mutations in a calcium channel.
Area of Impact (as written by the applicant)	Neuropsychiatric symptoms in TS have no targeted treatments and cause a change in the quality of life for the individuals and their families.
Mechanism of Action (as written by the applicant)	We designed an antisense oligonucleotide that reduces the expression of the TS1 variant. When it is expressed at a lower level, or not at all, then it has significantly less of a harmful impact on brain cells. We confirmed this in human pluripotent stem cell-derived neurons in the lab.
Unmet Medical Need (as written by the applicant)	TS1 heart symptoms can be managed with medications and a surgically implanted device called a cardioverter/defibrillator; however, there are no specific treatments to manage issues and no preventative cures for the brain symptoms.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Determine optimal dose in rodent for safety, pharmacokinetics/pharmacodynamics, and efficacy. • Determine safety, pharmacokinetics/pharmacodynamics, and efficacy in large animals at doses extrapolated for human use. • Determine on- and off-target effects on gene expression to suggest biomarkers for clinical trials
Statement of Benefit to California (as written by the applicant)	Given how rare this disorder is and that we are not currently aware of any living individuals with TS1 in California (though we will continue to search), this treatment may not directly benefit citizens of the state who have TS1. Supporting a first in human treatment for TS1 will benefit the State of California in general by advancing medical discoveries, bringing individuals with rare disorders to California medical centers, and raising the academic profile of California institutions.
Funds Requested	$6,112,230
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	4
Highest	85
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	2
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/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	• Yes. Timothy syndrome type 1 (TS1), also known as long QT syndrome (LQTS) type 8, is a rare, life-threatening genetic disorder whose symptoms include syndactyly, cardiac arrhythmias, and a high risks of developing neuropsychiatric disorders including seizures, developmental delay/intellectual disability, and autism. Although there has been progress in addressing cardiac symptoms (improving survival), significant unmet medical need remains because individuals with TS1 continue to experience debilitating neurodevelopment and psychiatric symptoms for which there is no treatment. The product is a TS1 antisense oligonucleotide (ASO), which the applicants state will prevent the development of and/or improve pre-existing neuropsychiatric symptoms such as developmental delay, seizures, and autism spectrum disorder. However, little evidence is provided to support this claim. • Timothy Syndrome is a rare disease with a complex etiology resulting in cardiac arrythmia. Patients are often autistic and there are multiple associated developmental outcomes which manifest in other parts of the body such as webbed finger and toes. The underlying pathogenesis is complex. • This product could be impactful for an ultrarare disease. • The ASO product may impact an unmet need in a rare disorder (TS1). • If successful this treatment would provide a significant improvement in standard of care.
No: 2	• There will be very few patients to enroll in an eventual trial.
GWG Votes	**Is the rationale sound?**
Yes: 11	• Yes. The antisense oligonucleotide intervention for TS1 is designed to target the underlying pathogenic variant in in the disease-causing gene. The manufacturing and testing of the proposed ASO was not provided in detail, but the CMC for similar products exists. • The manufacture and testing of ASOs was not provided in detail, however the CMC for similar products has been proven (with the exception of product-specific potency). • The product has been manufactured at research scale.
No: 2	• The rationale suffers from the lack of ability to find or develop animal models that will provide confidence for patient acceptance for a clinical trial. • The plan to use an antisense oligonucleotide to target potentially multiple mutations was not considered a viable proposition to replace the protein(s) required for normal cell function. The target product profile was not adequately supported by nonclinical proof of concept data.
GWG Votes	**Is the project well planned and designed?**
Yes: 6	• Yes. All the steps are well thought through and designed to meet the next stages of development. However it is concerning that the applicants put a lot of emphasis on their product being able to reduce neurodevelopmental/psychiatric symptoms associated with TS1, while this is mainly speculative at this stage - there are no available and quantifiable biomarkers. • The detailed CMC plans were not provided.
No: 7	• CMC information is lacking. • There is insufficient preliminary data. • There are multiple gaps in the planned approach and plan to establish efficacy and safety. CMC was not well-planned.
GWG Votes	**Is the project feasible?**
Yes: 9	• Yes, the project is well planned and achievable within the proposed timelines, although tight. • The plan is reasonable. • Plans are not provided in detail, but the timeline provided should be commensurate with handling risks to CMC. • The applicants state that they have identified several risks to project success on the intended timeline, including early target failure, unsafe toxicology results or other off-target safety concerns, therapeutic window, etc. They do not provide any details about mitigation plans except stating that they identified consultants and industry leaders to serve as guides if they will need to alter development plans.
No: 4	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**

Yes: 13	• Yes. The applicants propose to use animal models of both sexes. Timothy syndrome is not known to be more common in one gender or to be more common in any ethnic, racial, or geographic location. • The applicants state they will meet with the Timothy Syndrome Foundation and the Timothy Syndrome Alliance to ensure that their clinical project development addresses concerns and meets the challenges and needs of individuals with TS1. They plan to do a needs assessment to understand patients/caregivers perspectives on what neuropsychiatric symptoms they hope will benefit from ASO treatment, what biomarker measurements and ASO delivery strategies would be acceptable and tolerable, and how to be engaged and equitable in participant recruitment. • The incorporation of DEI was adequate. • DEI was adequately addressed given the rare disease indication metrics.
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

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	5	• The applicants include the following future activities in their DEI plan:
		  • DEI-specific consultants
		  • Testing in both male and female animals
		  • Language interpreter services
		  • Assessment of expected outcomes with patient support organizations and caregivers
		• The application includes a good DEI plan.
		• There is adequate DEI incorporation for the proposed project.

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

Application #	TRAN3-15331
Title (as written by the applicant)	Spinal subpial injection system for delivery of gene-based therapies in humans.
Translational Candidate (as written by the applicant)	Spinal subpial injection system for delivery of gene-based therapies to treat neuropathic pain.
Area of Impact (as written by the applicant)	Neuropathic pain
Mechanism of Action (as written by the applicant)	The proposed system is an instrument designed to deliver gene therapy to the targeted spinal cord segments. Spinally-targeted therapies for the treatment of segmentally-defined neuropathic pain require spinally-restricted delivery of therapeutic(s).
Unmet Medical Need (as written by the applicant)	At present, no injection device which would permit a spinal segment-targeted delivery of treatment vectors is clinically available.
Project Objective (as written by the applicant)	Pre-IND meeting held, FDA clinical use pending.
Major Proposed Activities (as written by the applicant)	• Regulatory - Completion of the Device Master File for the Surgical Platform • Regulatory - Completion of the Device Master File for the XYZ Manipulator • Device Development - Complete Bench and Biocompatibility Testing and compatibility and safety of vector therapeutic candidate for the Subpial Needle
Statement of Benefit to California (as written by the applicant)	A significant number of Californians are suffering from chronic pain. New treatment options are desperately needed for patients who fail standard therapies. This spinal subpial injection system (SSID) for spinal delivery of pain-alleviating genes will allow Californians to be at the forefront of spinally-targeted therapies to treat chronic neuropathic pain. SSID could improve the urgent national need for a new non-opioid-based anti-nociceptive therapy.
Funds Requested	$2,606,723
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	2
Highest	80
Lowest	75
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 13	• The applicant clearly identifies an unmet need for a technology that can provide discrete sub-pial injection in a controlled manner to deliver gene therapy to a very specific region of the spinal cord to target neuropathic pain. • Neuropathic pain, especially complex, regional pain syndromes and/or pain associated with spinal cord injury (SCI) is a vexing problem. Effective treatment of this problem would be broadly adopted. • This proposal aims to address the delivery of gene therapies for central nervous system (CNS)-based genetic disorders, where there is a substantial unmet clinical need. • The current application focuses on the development of this device as part of a combination product intended for an IND (investigational new drug) application for AAV treatment of neuropathic pain. • The primary novelty of the proposed device is the delivery of therapeutic substances (AAV in the current plan, but shRNA in other proof-of-concept animal studies) through a subpial system that employs an L-shaped needle. This needle is inserted into the subpial space, eliminating the need for parenchymal needle penetration. • Gene/drug delivery devices for treating CNS-based diseases are much needed. • This is a very complex regulatory plan - the device, if approved, will be a component of a combination product. Thus, the device itself will have minimal impact and/or use without a treatment for it to deliver. It becomes a chicken-egg problem in terms of regulatory and development issue. • Overall, yes, though the success of such devices is contingent upon the existence of gene-based therapies for delivery.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 11	• The rationale appears sounds based on the preclinical animal studies showing delivery and desired biodistribution of the AAV vector and expression of the encoded constructs. • Yes, the rationale for limited delivery of a gene therapy to the sub-pia space is sound. • The team has developed a strong body of data that show the delivery of the gene to the dorsal horn in NHP studies. • There are efficacy data in anti-nociceptive pain small animal models. • The rationale is supported by data provided by the applicant.
No: 2	• There are concerns about whether the device should be categorized as a combination product, which entails regulatory complexities, rather than as a stand-alone device. • Some gene therapies with strong potential would be limited by the utility and effective use of the device. • The project appears to have relatively soft criteria for success.
GWG Votes	**Is the project well planned and designed?**
Yes: 6	• The program is technically well-presented and the strategy for testing seems reasonable. • The project outlines a detailed plan for each of the device components. These plans seem well-designed and reasonable. • The quality program seems reasonable and follows appropriate design control principles. • The applicant has good guidance from FDA including a prior, related pre-IND meeting.

No: 7	• The project and proposal are well-designed, albeit necessarily incremental. The crux of this proposal is to develop a L-shaped needle interfaced to a micro manipulator for sub-pia injections. The studies proposed are indeed required, and many are interwoven with the biological (i.e., not device development related) studies. The data from the animal studies will also be used for the associated biologics program (which is a positive!). However, as currently written, the milestones require revision.
	  ◦ Milestones should be gating items. Filing a DMF with the FDA is not a suitable success criterion for a milestone. Instead, the applicant should specific Go/No Go success criteria that are dependent on FDA feedback.
	  ◦ In the current iteration of the Milestone 1, the FDA could return with a long list of hold items that may not be addressable within the scope of the project, and that would still be a GO. That is not acceptable as written, and should be revised substantially.
	  ◦ Milestone 6 is an example of a better, more quantitative read-out. In this milestone, the applicant uses quantifiable, percentage-based success criteria for retention of the vector.

	• The application needs to include at least one therapeutic for testing the device to merit funding.
GWG Votes	**Is the project feasible?**
Yes: 12	• This is a world class team and there is a combination of industry partners, CROs, etc. All of these are required for this type of activity. • The resources are available for successful completion of the program. • The project is milestone driven. However, the target product profile and plan to develop this product as a combination product need a closer look. • While the device plan seems feasible and well planned, the challenge with a combined product device development is that the success of the device development is inextricably linked with the success of the biologic drug, in this case AAV for neuropathic pain. The applicant separated their program into (i) this proposal for developing the device and (ii) a separate project for developing a gene therapy drug product. Success of (ii) directly impacts the feasibility of this proposal. • All necessary facilities and equipment are available. • There are some funds set aside for contingencies, but overall the contingency plans needs to be more clearly defined.
No: 1	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13	• The main issue will be to provide equitable access to the future trials. This is some way in the future. • The program has a community advisory board. The participatory pieces of this are not described. • The section on DEI appears suitable for device development at this stage. • The applicant's DEI response appears reasonable. • DEI was minimally but adequately addressed. • DEI plans are adequate.
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

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	7	• There is a great track record of DEI implementation at the applicant institution. • This proposal has adequate DEI incorporation for the proposed project. • Community engagement activities are well described. • Significant detail is missing, resulting in a lack of robust, planned efforts.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-15239
Title (as written by the applicant)	Autologous anti-PSMA CAR-T cell controllable by focused ultrasound (FUS-PSMACAR-T cells)
Translational Candidate (as written by the applicant)	Treatment of a subset of PSMA+, locally metastatic, solid prostate tumors
Area of Impact (as written by the applicant)	Prostate cancer
Mechanism of Action (as written by the applicant)	FUS-PSMA CAR-T cells will be administered as a fixed-dose intraprostatic injection in the tumor region. At two timepoints after CAR-T injection, FUS from a clinical device will be applied to non invasively and remotely generate mild hyperthermia in the prostate region.
Unmet Medical Need (as written by the applicant)	The prostate is positioned near critical organ structures. Surgery or radiation therapy targeting the whole prostate gland can cause severe adverse effects. Focused ultrasound (FUS) has been widely applied clinically for tumor ablation, but can cause neighboring tissue damage.
Project Objective (as written by the applicant)	Pre-IND
Major Proposed Activities (as written by the applicant)	• Generate GMP-like grade lentivirus using a GMP process for preliminary and IND-enabling studies. • Generate FUS-PSMA CAR-T cells and GMP-like grade lentivirus. Complete studies of T cell exhaustion and cytotoxicity in vitro. • Complete studies of FUS-PSMA CAR-T efficacy, persistence, and distribution in xenograft and mutant tumor models.
Statement of Benefit to California (as written by the applicant)	Prostate cancer is one of the leading cancers affecting males in America. Approximately 268,490 new cases were reported in America, with 26,890 new cases in California. Secondary to lung cancer, prostate cancer is the leading cause of cancer related deaths, which exceeded 34,400 male lives. Racial and ethnic disparities exist as African American males between 40 to 64 years of age are more likely to be diagnosed and are twice as likely to die of prostate cancer than white males.
Funds Requested	$4,449,448
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	77
Median	80
Standard Deviation	5
Highest	82
Lowest	65
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 10	• Estimating the impact of the proposed product is challenging due to existing treatment options for prostate cancer, including competing CAR-T clinical trials targeting PSMA. The potential impact may be specific to a subset of prostate cancer patients and could be linked to a better safety profile, specifically, reduced on-target off-tumor toxicity. • The success of focused ultrasound could extend to broader cell therapy applications if proven effective. • The applicant did not provide an overview of results from other CAR-T trials targeting the same PSMA antigen, which have been ongoing for nearly a decade and have shown limited success so far. • Conceptually, the technology could have a significant impact on targeting cell therapies. • The number of prostate cancer patients who would benefit from this therapy is limited given the current standard of care. • There is a major unmet need for new and potentially curative therapies for prostate cancer. • An autologous anti-PSMA therapeutic holds promise for making a substantial impact on the PSMA cancer population. • While the proposed product aims to address an unmet need, its potential impact depends on demonstrating clear advantages over existing therapies. The proposal shows that the system works, but it is unclear from the preclinical data whether there is a prospect of benefit over the standard of care. • At this stage, it is uncertain whether this warrants moving forward to a pre-IND stage. Conducting additional preclinical work would be beneficial to assess the potential for benefit. • The product has the potential for a significant impact on medically underserved communities.
No: 3	• The strategy addresses an important challenge in the field of CAR immunotherapy, namely antigen specificity, in an innovative way. The proposal comes from a well-qualified team that has a strong preliminary data related to the platform. However, significant weakness lies in the rationale - it is unclear if/how important this issue is for PSMA-targeted CAR T cells. • The primary goal of this highly innovative approach is to develop a therapeutic strategy to treat prostate cancer patients that would be more specific than the standard of care, radical surgery or radiation. Unfortunately, the investigators have neither submitted preliminary data, nor included in their proposed studies, data or experiments that truly address potential off-target effects of the proposed therapy. • This is a novel application, but the potential of the approach is unclear.
GWG Votes	**Is the rationale sound?**
Yes: 5	• The scientific and clinical rationale is sound. However, based on previous CAR-T trials in prostate cancer, the choice of PSMA antigen may not be the best. • A significant body of data is available in the application. The data appear to be of good quality. • There is no detailed information about focused ultrasound validation and parameters, which will be used in pre-clinical studies and will be translated to clinical trial. • Generally, the approach is very innovative and interesting: pairing the use of a heat shock promoter to express the PMSA-specific CAR with the application of focused ultrasound to generate a localized area of increased temperature. Unfortunately, the applicant has not provided proof-of-concept data demonstrating this spatial specificity. • Overall the rationale is sound, but PSMA as a target has been fraught with safety issues and unclear clinical impact. It's unclear how their proposed approach benchmarks against clinically tested PSMA CAR-T therapies in this regard.
No: 8	• The rationale for the application of this focused ultrasound platform to prostate cancer is uncertain. Off-tumor effects of current PSMA-CAR-Ts have not been reported. Recent clinical trials of immune cell therapies targeting PSMA have not shown evidence of off-tumor toxicity, even where there is evidence of efficacy. This may be due to relatively lower expression of PSMA in normal tissues as compared to prostate tumors. The

	investigators do not establish the need for additional safety engineering in the context of PSMA-targeted therapies. • The platform may have future impact in safety of CAR-T therapies, but in limited contexts or in combination with other immune-stimulatory therapies. Such strategies are yet to be defined. • Local prostate cancer, as opposed to metastatic, castration-resistant disease, does not present a huge unmet medical need. • The scientific background is sound and detailed. Current evidence appears convincing, but only demonstrates that the pieces of the system work. Proof of concept for effectiveness is needed. • The scientific rationale is not supported with sufficient data on efficacy or safety. • This platform is limited to localized (not metastatic) disease, which limits its utility.
GWG Votes	**Is the project well planned and designed?**
Yes: 7	• The project appears well planned. • This is a good team and they provide good preliminary data. The application includes insufficient detail on the ultrasound technique. • The "leakiness" of the system is not well addressed. For instance, heat shock promoters respond to stressors other than temperature, but these are not addressed. What is the promoter activation at a range of temperatures? • In the in vivo experiments (Milestone 3) the CAR-T cells are delivered twice. If there is an expected efficacy advantage to the platform, perhaps only one infusion would be better for evaluating efficacy/persistence as compared to the standard CAR-T?
No: 6	• The application does not include sufficiently detailed plans for the regulatory pathway for this combination product. • In their studies the applicant demonstrates lack of effect at a distal tumor site, not lack of off-target effects. The applicant should follow the specific recommendations in the FDA Guidance, Consideration for the Development of CAR T Cell Products, which includes clear recommendations for studying off-target effects. At a minimum, the applicant should perform analysis of cytotoxicity on a panel of primary human cells that are not tumor cells. • The proposal does not adequately address spatial specificity within the prostate. The applicant should discuss and address potential for local toxicity to normal cells. • The proposal does not include an appropriate back-up strategy if the nonclinical plan fails. Re-developing the whole vector would not be commensurate with cost and timelines. • Overall, yes, the plan is detailed and thorough, particularly for the cell component. There is no device information in the proposal. There is little information regarding a development plan for the device portion, regulatory strategy, or data being generated for the device. • It is not clear that the industry partner has committed to providing letters of authorization for use of data in an IND filing. Is this is the right device partner going forward? • At this stage the applicant should assume that FDA will regulate the proposed platform as a combination product, and will require full supporting information on the device component in the IND filing.
GWG Votes	**Is the project feasible?**
Yes: 10	• The timeline may be too aggressive since there is a risk of delays with GMP vector production. • There is some uncertainty related to the provider and manufacturer of ultrasound equipment. It is not clear how much support the team can get from the company when it is time for equipment optimization for the trial. • The project appears to be planned to achieve meaningful outcomes; however, it is not clear that it includes all activities necessary to advance to a pre-IND.
No: 3	• One of the risks the applicant identifies is related to CAR-T manufacturing at their chosen manufacturer. Their mitigation plan is to use/develop a different manufacturing strategy and/or different manufacturer if needed. However, they've set aside $250,000/year as back-up funding, and the cost estimate for manufacturing is about $1.5 million. Their contingency funds would not be sufficient to allow them to seek manufacture by another facility. • There are significant limitations. The application doesn't demonstrate clear knowledge of the regulatory process for a combination product.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12	• The DEI aspects of the project are sufficient, though the proposal is vague in describing some of the programs that they suggest would address the DEI principles. • The applicant has approached this thoughtfully, but the application does not include many concrete plans for consideration.

	• DEI is adequately addressed.
No: 1	• DEI plans are relatively non-specific, apart from inclusion of a Key Person who is running a trial that is actively recruiting African American men.

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	0	*none*
6-8: Responsive	6	• The proposal includes adequate DEI incorporation for the project. • Cancer is an unmet medical need with large underserved communities. • There is reason to believe a future trial will be designed specifically to be inclusive of Black men with prostate cancer. • The proposal is includes good DEI-oriented demographic data with regard to the target indication.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-15279
Title (as written by the applicant)	A novel gene therapy for the treatment of familial partial lipodystrophy disease type 2 (FPLD2)
Translational Candidate (as written by the applicant)	An AAV8 based gene therapy that overexpresses FGF21 and sTGFbR2 to treat FPLD2
Area of Impact (as written by the applicant)	FPLD2 is a rare disease with significant unmet medical need.
Mechanism of Action (as written by the applicant)	The candidate AAV8 gene therapy will overexpress two proteins to reverse or mitigate the primary and secondary disease. FPLD2 is characterized by dislipidemia, high glucose, high triglycerides and secondary comorbidities of end organ damage. FGF21 will focus primarily on the metabolic associated dysfunction and sTGFbR2 will predominantly mitigate fibrotic tissue development and end organ dysfunction.
Unmet Medical Need (as written by the applicant)	There are no approved therapies for FPLD2 in the US. FPLD2 mimics insulin resistance, with central obesity, hyperinsulinemia, and glucose intolerance. Multi-systemic effects include nonalcoholic steatohepatitis leading to liver cirrhosis, and acute pancreatitis. The candidate gene therapy will treat primary metabolic disease and secondary organ effects.
Project Objective (as written by the applicant)	Request pre-IND for alignment for IND readiness
Major Proposed Activities (as written by the applicant)	• Complete preclinical animal experiments that would support a successful pre-IND discussion with the FDA • Transfer AAV CMC process to CDMO for scale up productions • Obtain natural history and patient focused outcomes to inform clinical trial design for pre-IND discussion
Statement of Benefit to California (as written by the applicant)	FPLD2, an ultra-rare and life-threatening disease, has a significant impact on the lives of individuals in California. With an estimated 7,000 Californians affected by this condition, there is an urgent need for effective treatments. Our innovative regenerative gene therapy medicine aims to improve their lives, offering hope and a better quality of life. We are committed to addressing unmet medical needs and making a tangible difference in the lives of Californians affected by FPLD2.
Funds Requested	$4,000,000
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: 80

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

Mean	77
Median	80
Standard Deviation	4
Highest	80
Lowest	70
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 9	• Familial partial lipodystrophy 2 (FPLD2) is potentially lethal for individuals with this ultra-rare disease. • The project will target an ultra-rare disease which appears to be under-diagnosed within the population. An anticipated 7,000 Californians may exhibit LAMIN A/C mutations that have been previously un-diagnosed, given the broad-based metabolic symptoms associated with the pathogenesis of the disease. • The product may provide a treatment option for the ultra rare disease FPLD2, but is not curative.
No: 5	• It is unclear why the approach will not treat the causative mutation, which may have a potentially greater impact on the disease. • FPLD2 is a very rare disease but severe.
GWG Votes	**Is the rationale sound?**
Yes: 9	• The approach is to alter orthogonal genes that may mitigate the disease symptoms. • The CMC plans are sound, however the two growth factors selected may require further proof of concept.
No: 5	• The applicants intend to treat with a bigenic-AAV platform that is not intended to target the causative gene mutations but to target growth factors that may be indicated in the pathogenesis of disease and its progression. • The rationale is limited given the diversity of symptoms associated with this complex metabolic phenomenon. The concerns are related to lack of specificity of the clinical target and the potential for significant off-target effects based on the intravenous route of administration. The approach could potentially be considered unsafe by regulatory bodies.
GWG Votes	**Is the project well planned and designed?**
Yes: 9	• The objectives appear appropriate for the program to progress to an initial FDA interaction. • The timeline appears very aggressive, especially with CMC activities. • The application is too aggressive on the CMC timeline. Manufacturing and testing will take much longer and the applicants will likely be unable to parallel path other activities as aggressively as indicated. • The expression assay should be a sufficient measure of potency at this stage, but as there is no reference standard yet, the assessment against a reference is unlikely.
No: 5	• The nonclinical study plan looked broadly at renal failure and heart failure mouse models which showed low-to-moderate effects of treatment. The LMNA knockout animal showed limited effects on triglyceride levels, a key target in disease progression, and an effect on insulin resistance. In canines, there was a reduction in right atrial size that was observed up to 32 months, but target specificity was unclear. The planned nonclinical studies to establish dose in LMNA KO mice and pilot safety and distribution are unlikely to significantly advance the program.
GWG Votes	**Is the project feasible?**
Yes: 10	• The program is technically feasible. The question is whether the ultra-rare nature of the disease will be sufficient to support the funding needed to bring the program to commercialization. • The therapeutic concept may limit feasibility.
No: 4	• The project follows an ambitious timeline. • It is insufficient to broadly target heart or renal failure models with this product. There was concern related to off-target effects of the bigenic product.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 14	• The applicant appears to be aware of the requirements for incorporating principles of DEI as the project progresses. • DEI is adequately addressed.
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	4	• This is an ultra-rare disease that has been identified in fewer than 500 patients worldwide. • An international chart review found females represented about 75% of partial lipodystrophy cases, and women with FPLD2 present with a more severe phenotype. • In this review, the applicants note that 75.5% of patients were white, 13.3% were Black or of African descent, 6.1% were Hispanic or Latino and 6.1% classified as “other.” However, these demographics have not been correlated with clinical outcomes. • The applicant notes the existence of Lipodystrophy United which runs the Lipodystrophy Connect registry, indicating an intention to understand the patient perspective. • The applicants plan to establish patient advisory boards that are representative of CA's demographics. • The applicant notes that they will develop a diversity plan to improve enrollment of participants from underrepresented populations and will follow the FDA draft guidance for industry on clinical trial diversity issued in April 2022 to guide this process. • The applicant organization describes themselves as a culturally competent company that embraces diversity and actively works to create an inclusive environment where individuals from different cultures, backgrounds, and identities feel respected, valued, and supported. • The application describes how the organization's leadership team are involved in various efforts supporting equity and access to healthcare and therapies. • The application included great DEI incorporation for the proposed project.
6-8: Responsive	2	• The application includes solid data supporting their DEI approach.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-15213
Title (as written by the applicant)	In situ vaccination with chemokine genes CXCL9 and CXCL10-engineered dendritic cells for non-small cell lung cancer
Translational Candidate (as written by the applicant)	Chemokine genes CXCL9- and CXCL10-engineered dendritic cells.
Area of Impact (as written by the applicant)	Advanced stage non-small cell lung cancer (NSCLC) refractory to current immunotherapy.
Mechanism of Action (as written by the applicant)	The intratumoral injection of chemokine genes CXCL9- and CXCL10-modified dendritic cells (CXCL9/10-DC) will restore tumor antigen presentation and promote T cell infiltration and activation to enhance anti-tumor immune responses and overcome resistance to PD-1 (immune checkpoint) blockade.
Unmet Medical Need (as written by the applicant)	Although immune checkpoint blockade (ICB) is now the first-line treatment option for advanced stage non-small cell lung cancer (NSCLC), many patients do not respond and others progress after initial responses. Innovative strategies are needed to improve the response to ICB in NSCLC.
Project Objective (as written by the applicant)	Establish reagents and documents for phase 1 trial
Major Proposed Activities (as written by the applicant)	• Obtain GMP-grade lentiviral stock and establish potency assays. • Demonstrate in vivo kinetics and efficacy in multiple murine models. • Conduct a well-prepared pre-IND meeting and develop a clinical plan.
Statement of Benefit to California (as written by the applicant)	Non-small cell lung cancer (NSCLC) is the leading cause of cancer mortality in the U.S. and California. The current application focuses on a novel therapy of in situ vaccination with chemokine genes CXCL9 and CXCL10-engineered dendritic cells to improve the clinical efficacy of current immunotherapy. The successful translation of this strategy will improve clinical care and outcomes for patients with advanced stage NSCLC and benefit the State of California and its citizens.
Funds Requested	$6,300,700
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	77
Median	75
Standard Deviation	4
Highest	86
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	1
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 11	• The proposed product is designed to treat advanced lung cancer, particularly primary lung cancer that is refractory to immune checkpoint blockade (ICB) therapy. This is a significant unmet medical need. • As many as half of patients with NSCLC are either refractory to or become resistant to ICB therapy. The hypothesis is that this product can help overcome this resistance when used alongside ICB (anti-PD-1). • The most promising value proposition lies in combination treatments involving this cell-based therapeutic product use in conjunction with ICB. • Additional adjunctive therapies for NSCLC would have a profound impact, considering the unmet need for treating this highly aggressive cancer. • Overall, yes, but the absence of any responders in a previous trial using DCs expressing two other chemokines is a major concern. It may be preferable to explore new chemokines, as proposed here, but there is still limited evidence that DCs can elicit enhanced therapeutic effects.
No: 2	• Does the product use dendritic cells only as vehicles for delivery of the chemokines? Dendritic cells are a complicated platform to use and, if used, should be fully utilized for their pAPC potential.
GWG Votes	**Is the rationale sound?**
Yes: 7	• The scientific rationale underpinning this project is sound. • The application is packed with supportive preliminary data. • The quality of the data presented in the application is high, substantiating the proposed development plan effectively. However, a notable gap exists in the application regarding the description of the manufacturing process for the final drug (i.e., dendritic cell) product. • The approach taken is complex, yet the team has conducted an extensive series of studies across various models, demonstrating a notable anti-tumor effect. However, there is a legitimate concern about the translatability of these findings from murine models to humans. • While the rationale appears solid, some deficiencies in the application require revision. This is crucial to instill confidence that the project can progress successfully to a pre-IND meeting.
No: 6	• It's unclear whether the proposed administration method will effectively reach the target - the tumor microenvironment. • The rationale for why this new combination of chemokines will be more effective, when a prior set appeared to increase T cell infiltration, needs further support. Perhaps including a model study wherein the previously tested chemokines fail, while the new ones, CXCL-9 and CXCL-10, succeed, would provide a stronger argument for their development. • The mechanisms through which these cytokines would work are not clearly explained. While there are interesting preliminary data, there isn't a compelling argument that administration of DCs expressing CXCL9 and CXCL10 would be a game-changer for the treatment of NSCLC. • There are experimental systems, such as primary human cancer material (particularly tumor slices) which could more directly assess the impact of cytokines on the tumor immune microenvironment. Exploring these systems might be worth considering for this research. • It's uncertain if injecting 5 mm^3 tumors, particularly those subcutaneously implanted, will be relevant to human lung tumors. The relevance of this model to human lung cancer should be addressed.
GWG Votes	**Is the project well planned and designed?**
Yes: 5	• The project is well-designed and appropriately planned. • Yes; however efficacy data from studies with injection of larger tumors or more physiologically relevant models would be preferable.
No: 8	• The proposed timeline appears overly aggressive, particularly with regard to the data needed for the pre-IND meeting. Meeting regulatory requirements typically necessitates more time, and it's crucial to ensure that all necessary data are ready at least four months before the meeting. • While the planned IND-enabling studies seem generally on the right track, and there are a few strengths such as the early development of a potency assay, there are also some significant concerns:

	● The relevance of the proposed animal studies, particularly the use of non-immunodeficient models, needs clarification. ● Lack of manufacturing information about the transduced DCs. ● The absence of information on how integrated vector copy numbers will be evaluated to determine the optimal MOI (Multiplicity of Infection) for safety and efficacy. ● The suggestion of using the Animal Rule, which may not be applicable to this clinical indication, requires regulatory advice. ● The suitability of the chosen animal model for demonstrating clinical applicability of this treatment is questionable, especially for metastatic lung cancer foci. It's important to consider whether intratumor injection is a practical approach for this indication. ● The animal model should have better applicability to the clinical situation, and be sensitive enough to demonstrate whether this approach will be efficacious when other, related therapies have failed. ● There are several deficiencies in the plan: ● The request to consider the Animal Rule in lieu of nonclinical studies is not applicable from a regulatory standpoint. ● The plan for treating lung cancer cell trafficking is technically complex and needs further clarification. ● The CMC (Chemistry, Manufacturing, and Controls) plan is lacking in specifics. ● The approach to culturing dendritic cells is unclear. ● The need to conduct nonclinical efficacy and safety studies in immunocompromised animals is not adequately addressed.
GWG Votes	**Is the project feasible?**
Yes: 9	● The timeline of the project is appropriate. ● The team is qualified to perform the proposed work. ● The team has all the necessary resources to conduct the work. ● The applicant needs to consider and address the competitive landscape for enrollment into future clinical trials. ● Yes. This is a highly qualified team. The proposal includes a viable contingency plan with contingency funds secured from other sources. ● The project is feasible given the prior translation of a related DC product. However, the rationale for using DCs as opposed to viral vector or nanoparticle delivery of chemokines is unclear. Presumably the choice of DCs is due to the intrinsic ability of DCs to present antigen and elicit epitope spreading. However, no preliminary data related to this mechanism are shown. Do the proposed DCs traffic to lymph nodes after administration, and prime T cell responses? ● Potency studies seem ahead of schedule for the current stage of development.
No: 4	● There are insufficient specific plans for cell manufacturing. ● The study plan and design needs to be revisited.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13	● Yes, to the extent that this proposal is primarily for nonclinical studies and preparatory work for a clinical trial. ● The applicant has evaluated issues around DEI and understand that there are important socioeconomic and racial factors that impact both disease incidence and likelihood of receiving effective therapeutic treatment. ● From this analysis they've seen that Blacks and Hispanics high higher risk of disease and lower likelihood of receiving effective treatment. ● To ensure their therapy will be effective in these populations, they plan to obtain PBMC from individuals from these demographic groups to use in their potency assay. This is an important first step to evaluate the potential for effectiveness in these more diverse impacted patient populations. ● They also recognize that most patients who develop NSCLC are older, so their studies will be conducted in young and old mice. ● Additionally, the applicant should include plans to develop clinical plans that are balanced and inclusive with regard to these underserved groups. ● There are several different programs through the applicant's institution that have active engagements with underserved patient populations. ● The applicant's specific plans and the programs at the applicant's institution suggest that this project upholds principles of DEI. ● The project upholds principles of Diversity, Equity, and Inclusion (DEI). ● The subject of DEI was adequately captured and well-addressed.
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	5	• The applicant provides an excellent summary of the health disparities in NSCLC associated with age, gender, ethnicity, and socioeconomic status. • The applicant plans to incorporate age, gender, and ethnic groups into product development utilizing patient samples and preclinical murine models. • The applicant will utilize the excellent DEI resources that are available at the institution, including a program specifically addressing community engagement in research. • Members of the research team have access to veterans as potential participants in future clinical trials. • The applicant plans to work with a CIRM-funded Alpha Clinic to enhance the recruitment of a diverse sample of patients for future clinical trials. • This is a strong, comprehensive DEI plan. • Adequate DEI incorporation for the proposed project.
6-8: Responsive	1	*none*
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-15336
Title (as written by the applicant)	Effect of Inflammatory Secretome on Epidermal Progenitor Cells
Translational Candidate (as written by the applicant)	Topical adenosine antagonist
Area of Impact (as written by the applicant)	Linear Scleroderma Morphea
Mechanism of Action (as written by the applicant)	The novel compound is an adenosine antagonist that inhibits fibrosis and alters the cellular micoenvironement to promote the proliferation of epidermal progenitor cells that allows for skin healing.
Unmet Medical Need (as written by the applicant)	There is no cure for morphea, and the current treatments have limited clinical efficacy and as such there is a major unmet clinical need.
Project Objective (as written by the applicant)	Pre-IND meeting with the FDA
Major Proposed Activities (as written by the applicant)	• Scale up manufacture of the therapeutic candidate. • GLP Toxicity studies for Pre-IND meeting • Bleomycin induced scleroderma model
Statement of Benefit to California (as written by the applicant)	The proposed treatment provides a first-in class therapeutic to ease the disease burden of a clinically unmet need, Scleroderma morphea is disease that is biased to women and some minority groups and this will provide a treatment.
Funds Requested	$1,945,600
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	4
Highest	84
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/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	• This is an application that aims to study a topical compound for the treatment of morphea. For clinical context, morphea is rare – incidence is a few cases per 100,000. It can be quite morbid disease, but typically does not impact mortality as it is only limited to the skin; in some rarer instances morphea can impact the deeper soft tissues. The standard of care in treating patients with morphea is reducing inflammation – either topically with corticosteroids, calcineurin inhibitors, or phototherapy or systematically with agents such as methotrexate or mycophenolate. The prognosis for morphea is in general quite good, although scarring and disfigurement can be long-term complications. • The compound is a non-specific adenosine receptor antagonist that promotes growth of epidermal progenitor cells. The compound was developed by analyzing the secretome of activated fibroblasts to determine what compounds inhibit fibroblast activation. • I think this product has good potential. The compound discussed in this application is appealing because it targets fibrosis itself, not just inflammation, and can potentially reverse scarring – this is very appealing and no other agent can really do this in the morphea treatment landscape. Currently, even in patients who are "successfully" treated, patients often have a chronic 'burnt out' lesion that is different in texture (sclerotic/dystrophic) and often discolored. This often has emotional (and also possibly functional) consequences, particularly for young children. • One potential concern from a clinical perspective is the ability for the compound to cross the blood brain barrier (BBB); the proposal only really describes BBB penetration in relative terms (e.g., 50% risk reduction), not the absolute amount. What is the absolute amount/concentration of drug that crosses the BBB and what is the threshold that is needed to produce cognitive effects in children and adults? With a cream applied twice daily (meaning one application at night) to a population largely of children, I'd want to know what the BBB absolute concentration is and whether this is predicted to have cognitive impact. • As a topical agent, it would not be applicable to generalized morphea (up to a third of all morphea patients), where the body surface area involved makes a topical agent impractical. It is also unclear whether the cream would/could be applied to sensitive areas (face, genitals) and whether this would be assessed in the proposed toxicity studies. • Conceptually, additional therapeutic options would be helpful. Based on stage of development though, it may be challenging to assign value proposition based on unclear efficacy, dosing regimen (and thus associated required clinical care), etc. • Morphea is a rare disease. The therapy could potentially could reverse scarring.
No: 4	• The application was not sufficiently well-written to ascertain the potential impact of the project or the target product profile. • A topical approach does not seem like the best approach for patients. A systemic agent seems like a more patient-friendly approach.
GWG Votes	**Is the rationale sound?**
Yes: 9	• The rationale is supported by preliminary data. • The anti-fibrotic potential of the product is perhaps its most compelling feature. • There is a body of evidence to support these types of therapeutic approaches, although it is challenging to evaluate preclinically. • There is some evidence, but this is limited in some key areas; providing more proof of concept data would be useful.
No: 4	• The project was presented with an ill-defined mechanism of action and appeared to be rushed. The data presented to target fibrosis and reverse scarring was not well explained and key details on the proof-of-concept and planned studies were not sufficient to indicate a sound rationale. • Previous data in healthy mice demonstrated reduction in scar size and collagen deposition, without any clear evidence of cardiotoxicity based on monitoring of heart rate or arrhythmias. • When describing their preliminary data, the researchers note they obtained fibroblasts from a patient with keloids. Keloid is not the same thing as morphea, and thus this is a bit of a leap extrapolating experiments on keloidal formation to morphea. Further, fibroblasts from a single patient seemed inadequate to draw robust conclusions (for both efficacy as well as safety i.e., cardiotoxicity). At least three patients would be ideal.
GWG Votes	**Is the project well planned and designed?**
Yes: 4	• The objectives are appropriate. • Considering the low relative risk of the proposed product, it is possible that the preclinical development of this product could be accelerated. It may be such that the true value proposition of this product is unclear until initiation of human clinical testing, thus, a more streamlined approach to development with gated spends is recommended.

	• Applicant should consider getting FDA feedback much earlier in development. The applicant should not conduct the proposed toxicology study prior to pre-IND feedback. It is quite likely that FDA will advise a very different study and/or development pathway. • It may be reasonable to prioritize completion of additional pharmacology/proof-of-concept studies in dermal wound healing mouse model and wound healing model in the animal model, followed by FDA feedback on continued development. It is not recommended that the applicant conduct any additional safety or toxicity studies until after additional pharmacology / proof of concept studies are completed and FDA feedback is received. • I would like to see the initiation of some of the proposed activities gated to successful completion of previous milestones; this will help mitigate some of the risk inherent in the proposed approach and ensure efficient allocation of resources.
No: 9	• The applicants do a good job describing their approach, plan, and timeline. The team appropriate leverages the expertise of a renowned clinical expert with a wealth of experience in morphea and related outcome measures. • Limited preliminary data (in keloid scarring). • Not enough detail was presented to indicate a well-planned program. • The overall feel of the application feels rushed given the number of grammatical errors.
GWG Votes	**Is the project feasible?**
Yes: 9	• As proposed, the immediate objectives are feasible. The competitive landscape should be considered. • Technically the project is feasible with greater attention to detail on the plan for nonclinical and CMC components. • Recommend changing order of milestones and gating of some activities until after pharmacology/proof-of-concept studies are completed to justify further development; recommend waiting on any safety/tox studies (even if they are pilot studies) until after FDA feedback. • The timelines seem a bit aggressive.
No: 4	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12	• From a DEI perspective, as the applicants point out, morphea is a disease that impacts both women and men, adults and children, and all races. A topical cream could be easily applied and would not require transportation or proximity to a city (as is often the case for those patients who are prescribed UV or phototherapy to treat their morphea). It is good that they are employing a community outreach contractor to raise awareness and engage with community clinics. • Appears to be appropriate for this stage of development. • DEI was addressed adequately. • DEI appears to have been addressed minimally.
No: 1	*none*

DIVERSITY, EQUITY, AND INCLUSION (DEI)

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

DEI Score: 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	5	• There is adequate DEI incorporation for the proposed project. • Better discussion on the impact of product development would help.
3-5: Not fully responsive	0	*none*

0-2: Not responsive	0	*none*

Application #	TRAN4-15342
Title (as written by the applicant)	Modular robotics cluster for the automation of cell therapy manufacturing
Translational Candidate (as written by the applicant)	A modular robotic cluster for the manufacture of cell therapies at scale, with data collection in the digital batch record.
Area of Impact (as written by the applicant)	The robotics cluster addresses the scalability of cell therapy manufacturing, bioinformatics and cell handling.
Mechanism of Action (as written by the applicant)	The robotic cluster is an autonomous system for the manufacture of cell therapies at an industrial scale. The innovative technology is composed of a highly modular system that leverages automation and uses standard GMP equipment. A patented closed-system consumable set enables the use of robots to perform activities otherwise performed by skilled scientists. The cluster is controlled by a cloud-based software, recording every data in the Digital Batch Record and interfacing with the factory MES.
Unmet Medical Need (as written by the applicant)	The robotics cluster enables scaling cell manufacturing thanks to a higher density of bioreactors, lower labor requirements, and higher quality by removing human errors and contamination risks. Every robot action and sensor data is accessible via our SW and recorded in the Digital Batch Record.
Project Objective (as written by the applicant)	Readiness for transfer to manufacturing
Major Proposed Activities (as written by the applicant)	• Completed System Verification and Validation, Creation of the Design History File • Completed Manufacturing Plan • Completed Commercialization Plan
Statement of Benefit to California (as written by the applicant)	The robotics cluster is designed, assembled and tested in San Francisco. Our consortium partners are also located in California. The outcome of the project will enable the production of cell therapies to support the needs of a large population at lower costs, bringing benefits to the patients and the broader health system in California.
Funds Requested	$1,349,069
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	5
Highest	80
Lowest	60
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/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	• Developing robotics for cell therapy production has the potential to significantly impact the quality and cost of these products. • The proposed robotic cluster aims to provide an end-to-end automated production line for cell therapies, both autologous and allogeneic. While interesting, it faces competition from similar products already available in the market. • The proposal does not convincingly demonstrate that this product will accelerate the development of stem cell technology to significantly improve patient care. It is unclear what advantages this particular product offers over existing solutions. • The proposed robotic cluster is an innovative system designed for industrial-scale cell therapy manufacturing. It boasts a modular design that capitalizes on automation and a patented closed-system consumable set, allowing robots to handle tasks typically done by skilled scientists. This results in reduced labor requirements, higher bioreactor density, increased throughput, and a lowered risk of contamination and human errors. The applicant claims to have industry support from key industry players. • If this proposal had been presented several years ago, it might have been immediately fundable. However, with multiple existing solutions on the market and the potential for more competition to emerge in the coming 18 months, the landscape has become highly competitive. • Some data presented in the proposal did not demonstrate equivalence to human-generated data, and further iterations of module manipulations may be needed to achieve or exceed human performance.
No: 9	• The proposal has limited novelty and faces competition from more advanced products in development. • It is challenging to see how the applicant can catch up to competitors or how broadly applicable this technology is beyond T cell manufacturing. • The project utilizes modular systems to expand the process for developing CD8+ cells. However, given the presence of numerous robotic systems on the market, this is not a high-value proposition, especially when limited to a single cell type. • There are concerns about the limited impact of the proposed work, focusing on a single-cell type that is not a therapeutic candidate.
GWG Votes	**Is the rationale sound?**
Yes: 10	• Yes. The project is backed by a sound scientific rationale. Furthermore, removing the need for a highly skilled staff would be greatly advantageous (and links to DEI). • The rationale appears sound but has limited utility. This is a robotics-focused grant as opposed to having utility in broad-based immunology-centric clinical indications. • The strength is that two robot arms can handle the equivalent of expert researchers in process development for T cell manufacturing. • The rationale for derisking the instrument is supported by the preliminary data.
No: 3	• Each product may have specific needs, requiring individual program validation. How will the regulatory filings manage the specifics for each product?
GWG Votes	**Is the project well planned and designed?**
Yes: 7	• The project is well planned with well thought-through timelines and milestones, but the data are not very compelling when compared to human generated data.
No: 6	• The regulatory pathway is not mentioned, advice should be sought. • There is limited focus on potential clinical uses, and the proposal did not address the global market space in its plans for development. • The design needs to address the modular nature of the platform better by showing how different operations or cell types could be manufactured. • Cell characterization of the manufactured cells needs to be more comprehensive.
GWG Votes	**Is the project feasible?**
Yes: 11	• This project is very ambitious. Though this is feasible within the proposed timelines, it will be tight to achieve all the goals. • The team is experienced. The contingency plans are well developed. • This appears to be feasible but with potentially limited utility. • The team is capable and has enough resources for this project.
No: 2	• It appears that the robot could not reproduce the quality of cells produced by the human technicians.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes:	• The DEI section appears appropriate for this product at this stage.

13	• The applicants have taken DEI into account when developing their project and have addressed it appropriately - as much as possible for this type of proposal. • Comprehensive. • DEI was comprehensively considered and well presented. • The DEI plan could connect to the research more directly.
No: 0	• This is not addressed and probably not relevant for robotic process development.

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	0	*none*
6-8: Responsive	6	• The proposal includes adequate DEI incorporation for the proposed project. • The proposed robotic system for the generation of cell therapies at an industrial scale could serve diverse populations. • This tool is agnostic to the ethnicity or demographics of the cells being cultured. • The proposal incorporates good data related to DEI. • This has a well-stated DEI plan.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN3-15223
Title (as written by the applicant)	Development of an endovascular bioartificial pancreas (eBAP) device for the treatment of type 1 diabetes
Translational Candidate (as written by the applicant)	Endovascular bioartificial pancreas (eBAP) device
Area of Impact (as written by the applicant)	Type 1 Diabetes
Mechanism of Action (as written by the applicant)	The mechanism of action of the proposed eBAP device encapsulating stem cell derived beta cells is sensing glucose from body tissues and secreting clinically relevant doses of insulin in response to regulate glucose levels.
Unmet Medical Need (as written by the applicant)	Type 1 diabetes is an autoimmune disorder that results in unregulated glucose levels for 1.9M Americans. We are developing a novel bioartificial pancreas device that contains cells that secrete insulin in response to changes in blood glucose, providing precise blood glucose control.
Project Objective (as written by the applicant)	Readiness for pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Optimize the eBAP device design to deliver and support the function and viability of a therapeutic dose of cells. • Stem cell derivation of islet-like clusters that have appropriate functionality and express endocrine markers of differentiated beta cells. • Test islet-like clusters in the eBAP device in-vitro and demonstrate clinical efficacy in a diabetic swine model.
Statement of Benefit to California (as written by the applicant)	Approximately 3,209,418 people in California have diabetes, of which 10% is attributed to T1D. The total direct costs of diabetes in California is $27B, with an additional $12.5B spent on indirect costs. This bioartificial pancreas device has the potential to improve quality of life, health outcomes, and life expectancy for these patients with T1D. This proposal also centers growing a California-based small business, supported by a network of expert contractors within the state.
Funds Requested	$1,961,058
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	73
Median	75
Standard Deviation	2
Highest	75
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/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	• If successful, the proposed product would enable treatment of Type 1 diabetes (T1D) by an allogeneic cell-based therapy without the need for immunosuppression. This would have a major impact on treatment of this disease. The value proposition is highly attractive. • The project has the potential to support a large unmet population in the US and California. • The concept of an artificial pancreas for treating and possibly curing diabetes is the holy grail. • There is some potential to further advance the T1D standard of care.
No: 3	• The proposal has limited novelty. • It's not convincing that they will be able to do what many others have tried and failed, especially given their limited cellular experience.
GWG Votes	**Is the rationale sound?**
Yes: 8	• A device loaded with stem cell-derived insulin-secreting beta-cells, protected from immune rejection but in close proximity to the bloodstream seems a practical concept with a reasonable rationale. • The data presented are encouraging but somewhat thin. Biomaterials and design features utilized in the device to enable long-term cell survival and diffusion out of insulin, without fouling and while rigorously excluding immune cells, are not fully rationalized. The long history of efforts to encapsulate islets indicate that this is a challenging proposition. Rapid fouling of devices is common. The goal of 10-year survival of functional devices, as stated as best case in the target product profile, seems extremely optimistic. • The rationale is scientifically sound but not commercially sound as the risk/benefit for these patients will require a durable response. • Comparison with other currently applied beta-cell therapies should be conducted. • Unclear at this stage of development.
No: 6	• The rationale was based on implanting devices which are pre-loaded with pancreatic islet cells and implanted arterially to enable survival in oxygenated blood. There would be a requirement for repeated interventions once the cells become depleted, which is not a high value proposition for patients.
GWG Votes	**Is the project well planned and designed?**
Yes: 6	• The CMC on the cell-derived drug product is heavy on characterization, but there is no indication that the sponsor is forward-thinking to cell product testing release or stability requirements. • Unclear, as many aspects of CMC are not well-defined or described.
No: 8	• The concept is logical and steps are laid out fairly clearly. The applicant focuses particular attention on device parameters to ensure sufficient oxygenation of enclosed beta-cells and release of insulin into the circulation. • Cell biological aspects of the project are given short shrift. The applicants cite a published protocol for differentiation of pluripotent stem cells to the pancreatic and beta-cell lineages. However, this is not a trivial process. The plan neither provides sufficient information on how it will be carried out and optimized for a clinical device, nor on optimization and quality control of the encapsulated islet-like cell structures. • Overall, the plan seems highly ambitious. There is no clear approach to ensure that the devices will be sufficiently long-lived to achieve the goal of maintaining stable glucose control over an extended period, at least as long and preferably much longer than has been possible to date after islet transplantation. • There was insufficient proof of concept to evaluate efficacy and the requirement for potential repeated implantation procedures was not considered. • The information about the cells and the encapsulation process is lacking. • Unlikely to finish in time.
GWG Votes	**Is the project feasible?**
Yes: 9	• The project may be technically feasible, but commercially may not be feasible. • Perhaps too early for a TRAN grant; additional supportive data required to support the probability of success.
No: 5	• Differentiation of highly functional, mature beta-cells from human pluripotent stem cells has been a major challenge for some years. However, there is now convincing evidence

	that it can be achieved. The design of the device also appears attractive. However, whether performance of the device can be maintained over a sufficiently long period to make this a medically and commercially viable product remains uncertain, constituting a significant risk. ● It was felt that the device could only potentially be feasible for a short duration and this would not satisfy the long-term goals for effectively treating Type 1 diabetes. From a CMC standpoint, there was no quality control of the cells or evidence of cell viability complicated by the capsules. ● The very ambitious nature of the project raises doubts that it can be accomplished in the proposed time frame. While contingency plans are presented, they do not sufficiently address the overall concern about feasibility. ● There are some very well-qualified, experienced consultants to the project, notably an emeritus professor with a long track record of work on islet transplantation and an expert in islet encapsulation. However, it does not seem that they have defined hands-on roles in the project. ● The team has reasonably strong qualifications "on paper," and the PI's biography, in particular, suggests a highly focused, innovative individual capable of achieving a big objective. However, the core team appears to have little practical experience in product development or, specifically, in research with stem cell-derived beta-cells and islet-like structures. ● Concerns about expertise on the team - would benefit from more experienced collaborators.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 14	● DEI does appear to have been effectively addressed. ● The DEI section is appropriate for this stage of development. ● A successful outcome would benefit the entire population, as Type 1 diabetes is a common disease across a highly diverse set of individuals. ● The applicant plans to incorporate education and outreach regarding DEI. However, there is not yet a clear track record of team members and their institution making proactive efforts to engage with the population that will benefit.
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	6	● Good demographic data by racial group and income, including mortality impact. Data informs product development assessment and direction as access to the procedure and the device is essential to creating a broad usage product offering. ● Adequate DEI incorporation for proposed project. ● Adequate DEI plan.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-15240
Title (as written by the applicant)	Development of cargocyte expressing IL-12 for the treatment of metastatic cancers
Translational Candidate (as written by the applicant)	The candidate is being developed to treat metastatic solid tumors where patients have no good options.
Area of Impact (as written by the applicant)	Metastatic cancers have no good therapeutic options. The candidate product offers an effective treatment option for late stage cancers.
Mechanism of Action (as written by the applicant)	The candidate product is a precision-delivered therapeutic that seeks out metastatic cancer cells and locally produces the potent immune-activating cytokine IL-12. Thus, the product minimizes systemic toxicity that has plagued IL-12 with traditional delivery approaches. The product overcomes critical manufacturing and safety concerns for cytokines.
Unmet Medical Need (as written by the applicant)	Powerful cytokines like IL-12 are too toxic to be administered systemically. Localized approaches are needed to utilize such immune modulators as therapeutics. The candidate product effectively localizes IL-12 within the tumor microenvironment offering treatment options for late stage metastatic cancers.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Development of a Good Manufacturing Process with quantitative control assurances. • Design a clinical trial addressing disparity equity and inclusion using a decentralized clinical trial approach. • Building a complete regulatory package for a Pre-IND meeting.
Statement of Benefit to California (as written by the applicant)	As an innovative platform, the cargocyte is a vertical move for science. Our organization continues to build our R&D team and plans on adding our biomanufacturing center at our headquarters in Carlsbad, CA. This proposed research will drive our manufacturing process and accelerate the growth of our company by an expected 100% in full time employees within two years.
Funds Requested	$3,183,602
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	72
Median	75
Standard Deviation	4
Highest	75
Lowest	60
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/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	• Advanced triple negative breast cancer (TNBC) represents an unmet medical need due to a lack of approved effective therapeutic options. • Metastatic cancer is very common and difficult to treat. • The "cargocyte" technology is very interesting. Because cargocytes are used as a vehicle for therapeutic agents, the applicability of this technology could be very broad. • A major critique is that the entire proposal is focused on the CMC (and the investigators provide a clear rationale of the importance of a CMC in ultimate IND approval), but it seems unrealistic that without any dose finding and true IND-enabling studies that this would be as quickly translatable as they propose. No in-vivo studies are planned to study dose/toxicity.
No: 4	• The technology may be synergistic with other therapy modalities. However, the ability to translate to clinical benefit is uncertain given the timeline to clinical trials and approval. • The planned therapeutic approach was not described adequately and clinical targets were not clearly identified.
GWG Votes	**Is the rationale sound?**
Yes: 6	• Yes, in theory, but little data were provided to support the rationale. • This candidate product in combination with anti-PD-L1 checkpoint inhibitor therapy (i.e., atezolizumab) for nonresectable, treatment-refractory metastatic cancers, specifically PDL1+ TNBC, could have the potential to improve therapeutic safety profile and survival outcomes and also significantly improve quality of life. • One of the main potential benefits, though the investigators did not mention this, is that this platform could work with other cytokines (not just IL-12); of note, they did not make entirely clear why IL-12 was chosen, which would strengthen the application as would preliminary data on utilization of the platform with alternative cytokines.
No: 8	• There is no good explanation for why IL-12 is the therapeutic agent of choice for TNBC. • A body of available data is heavily focused on unique "cargocytes" properties and less on the rationale for using IL-12 instead of other cytokines or chemokines. • There were limited data to support the concept.
GWG Votes	**Is the project well planned and designed?**
Yes: 3	• Overall, the project appears well-designed, though some details are missing. Also, a majority of project activities are outsourced to a third-party, which is not of particular concern but can be challenging in execution within the timeline. Notably, the applicant organization has established key partnerships with a third-party which has extensive experience with manufacturing GMP compliant somatic cell therapies as well as two consulting groups which have expertise in FDA guidance policies surrounding living drugs and biologics.
No: 11	• The plan for manufacturing improvements and process analytical development is not detailed enough. For example, the process of enucleation to generate cargocytes is not described (what centrifuge speed, for example). General cargocyte assays and assays specific to the candidate product are not described. For example, the applications should describe assays to assess enucleation efficiency, residual DNA, residual nucleated cells as an impurity, and a potency/functional assay for IL-12. • Milestone tasks are described in more general terms and are not well-detailed. For example, how the enucleation process will be changed from the manual (gradient centrifugation) to a closed system (single-use disposable) is not described. • Outsourcing will need critical oversight to be successful. The application would be strengthened with more plans for oversight. • The applicants are outsourcing almost the whole work to multiple third-party companies. • It is not clear how the FDA requirements for GMP manufacturing will be determined and met. • The application includes reasonable preliminary data, but the timeline may be too short. • The project was ill-defined from a CMC, nonclinical, and regulatory perspective.
GWG Votes	**Is the project feasible?**
Yes: 9	• The timeline looks reasonable assuming all contract organizations will work without delays.

	• The work is outsourced to multiple companies. The assumption here is that all contractors are well-qualified and have all the necessary resources. • The project is feasible but there are concerns about the degree of outsourcing. The entire proposal is focused on the CMC so it seems less likely to be translatable to a clinical trial in the proposed time frame.
No: 5	• The project is too dependent on external contractors (CMC). • There was insufficient data presented to support the project.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 14	• The applicants acknowledge TNBC in Black patients as an unmet need and discuss how a chosen contractor will address DEI in future clinical trials utilizing their proprietary de-centralized clinical trial platform. • A contractor will work with the applicant organization's management to establish a post-therapeutic follow-up and surveillance program that eases the financial burden of travel and medical related expenses for future enrolled clinical trial participants. ◦ However, as this project is focused on CMC, it's unclear whether the companies they have worked with have experience with strategies to engage underrepresented minority communities. • This appeared to be addressed but missed several points. • The DEI aspects of this application have potential although more specifics will be helpful later on, closer to clinical stage. Clear goals related to diversity and inclusion would help in measuring success of the plan.
No: 0	*none*

DIVERSITY, EQUITY, AND INCLUSION (DEI)

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

DEI Score: 7

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	5	• There is adequate DEI incorporation for the proposed project. • The application includes good demographic and socio-economic data.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN4-15225
Title (as written by the applicant)	Purification of Human Hematopoietic Stem Cells (HSCs) for Clinical Stem Cell Transplantation
Translational Candidate (as written by the applicant)	A 'modernized' version of the two monoclonal antibodies-anti-CD34 and CD90 (Thy-1), to purify cancer-free or T cell free HSC for transplantation.
Area of Impact (as written by the applicant)	The development of hematopoietic stem cell-based therapies for a wide range of diseases.
Mechanism of Action (as written by the applicant)	We will generate improved antibodies and protocols for the isolation of human HSCs. The importance of purifying HSC is to eliminate potentially harmful cells from the graft. Removing a donor's immune cells can prevent graft vs host disease (GvHD), and removing cancer cells will prevent their re-introduction into patients. Our goal is to develop a purification scheme utilizing the new antibodies and clinical cell sorters, to yield cancer- and T-cell-free human HSCs for a safer clinical transplantation.
Unmet Medical Need (as written by the applicant)	Transplantation of purified HSCs can offer curative-intent treatments for a vast range of medical conditions, including genetic blood disorders, cancer and autoimmune diseases. It can also induce transplantation tolerance to same donor regenerative cell therapy or organ transplant.
Project Objective (as written by the applicant)	HSC purification protocols for a pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Antibody engineering, production and validation, to generate the reagents for isolation of human HSCs. • Process development: we'll test and optimize HSC isolation protocols on every clinical sorting platform available to date. • Quality assurance: we will develop the tools to assess the yield of blood-forming stem cells, the level of cell viability, purity, and function.
Statement of Benefit to California (as written by the applicant)	The goal of this project is to generate and provide reagents for HSC purification in a non-profit setting for academic transplantation units, and free for underserved patient populations. Our aim is to be the driver to expand pure HSC isolation and transplantation for a variety of human diseases, beginning with CIRM Alpha Stem Cell Clinics. California residents who can benefit medically will have the first access to these investigational therapies which we hope will be implemented world-wide.
Funds Requested	$1,504,551
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	68
Median	65
Standard Deviation	7
Highest	83
Lowest	60
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/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	• Purifying stem cells further could potentially enhance a myriad of transplants particularly in non-malignant settings.
No: 11	• There are many FDA-approved allogeneic hematopoietic progenitor cell purifications based on CD34. • The project was not considered impactful because there are multiple CD34+ products available and technologies have advanced in recent years, so there is not a high unmet clinical need. • This application does not address an unmet need that is worth CIRM funding. Also, the license to the IP needs to be in place before investing in development, otherwise the ability to commercialize is at risk. This is a major issue. • There is already a CD34+ cell enrichment/isolation platform available. What is the significant benefit of getting to a more pure population? Is there clear evidence of disadvantage from other subsets (especially if you can given equivalent doses of the defined ideal population, which might mean counting CD90+CD34+ cells)? • Major issue with this proposal is three-fold: first, it does not address a major bottleneck or need in the field. We have GMP grade anti-CD34 antibodies for enrichment of HSCs. Likewise, there are published protocols for the GMP sorting of CD34+CD90+ HSCs. • It is assumed that distributing these antibodies and protocols freely to transplant centers will lead to their uptake. The transplant field tends to be conservative and there have been other areas of focus in the field to improve overall outcomes, such as reduced intensity conditioning. Also, unclear if a fully T cell depleted graft is always the best option for certain indications. For example, recent results of the phase III multi-center BMT CTN 1301 trial for leukemia demonstrated that although CD34 selection was associated with significant reduction in cGVHD, this benefit was offset by an excess of treatment related mortality, suggesting that by removing the T cells from the graft in order to reduce GVHD, "the price that we pay" is increased toxicity-related infections and decreased survival. Other studies have also shown an association between low levels of T cells and increased mortality (Small et al., 1999; Goldberg et al., 2017; de Koning et al., 2021). One company, for example, is working on a precision sorted graft that combines CD34+ cells with different subsets of conventional and regulatory T cells to increase graft versus leukemia and reduce graft versus host. • Our understanding of HSPCs has expanded in the last several decades since the original discovery that CD34+CD90+ cells enable engraftment. Additionally, the field continues to get more granular on the nature of HSPCs. Lin-CD34+CD38-CD45RA-CD90+CD49f+ for example is one proposed staining panel for HSCs. Interestingly, there is still limited knowledge of the role of many of these cell surface markers with respect to their biological roles in human HSPCs. • This program is an incremental improvement on a 20-year old therapeutic modality. • Limited novelty.
GWG Votes	**Is the rationale sound?**
Yes: 9	• Overall rationale is sound and is based on decades of research. However, there has been significant public and private funding to test this concept. Unclear how this proposal actually advances the science and our understanding of HSC biology. • The strategy is sound but unclear if current limitation to autologous stem cell rescue is contamination with tumor cells that leads to relapse in cancer patients. • Technically the rationale is sound, and the preclinical data was compelling. But the project did not address deficiencies associated with how understanding of graft vs leukemia has shifted in recent years with respect to how best to target the disease and which cells are most important. The grant application was not considered to be well-written or address the clinical need.
No: 4	• The long-term feasibility of the product is unclear given where the field is today. • Why would they think clinical flow cytometry based sorting would expand access to more centers? It seems magnetic/bead based sorting is already more widely available. • The proposal is based on updating the prior monoclonal antibodies. However, they don't provide a reference to this other component, nor provide their own data, showing that it

	will prevent the antibody-mediated cell killing that they show to be a problem with the existing form of the antibodies. ● The proposal provides data from an assay spiked with tumor cells to demonstrate that their system will purify to remove any spiked tumor cells. These data would have been more convincing to show that it's improved purity over existing approaches, if they provided a head-head comparison of other CD34+ cell purification strategies using the same spiked cell preparations.
GWG Votes	**Is the project well planned and designed?**
Yes: 7	● Overall milestones and risk mitigation plans are reasonable for this project. ● The team is outstanding with all the experience necessary for success.
No: 6	● The PI has an experienced cadre of scientists and support. ● The project does not seem well planned and designed. As noted above, they have not been at all specific about their plans for how they will modify the constant region of the antibodies. They also provide limited information under each of their specific aims; aim 2c appears to be incomplete. ● The monoclonal antibodies will be produced by a contract manufacturer. The PI claims that they will produced as GMP-grade, but according to the quote, these MAb would not meet FDA criteria, as described in the FDA Guidance: "Monoclonal Antibodies used as reagents in drug manufacture". While there are a number of criteria that are met such as low endotoxin levels, and other measures of purity and identity, the manufacturer doesn't include sterility testing or other adventitious agent testing, or testing for leachables from the protein A column. The applicant does not provide any information about additional testing they would do, other than functional testing. ● Some preclinical data are well presented, but the project is not well described and the clinical need fell short. ● Clarification and more information is needed to assess the plan. ● Grantsmanship is poor and raises concerns more generally.
GWG Votes	**Is the project feasible?**
Yes: 10	● The project is feasible with potential for impact. ● The resources are available. ● Data presented are from years ago. ● Technically this project appears feasible, but not novel enough with sufficient competition to decrease its potential impact.
No: 3	● There are insufficient details to assess feasibility. ● Their contingency plan is to just express the a form of the antibodies in CHO cells which does not address a major risk that they noted in their studies. ● Highly qualified team. The applicant institution has multiple facilities that will support the proposed work. ● The applicant states that "While the mAbs will initially be supplied by [the applicant institution] to advance the field, for long-term commercialization, [the applicant institution] and [for-profit institution] will need to "agree to grant non-exclusive licenses to entities that will use the mAbs and processes developed in this proposal." In terms of long-term feasibility of this proposal, this seems like an important business and strategic decision that needs to be finalized (i.e. the willingness of the two institutions to grant non-exclusive licenses) before actual work and resources are invested in advancing this project.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12	● DEI section appears appropriate for this stage of development. ● Yes, generally. The applicant uses metastatic breast cancer in their discussion. Metastatic breast cancer is higher in African American women, an underserved community. However, the proposal does not address the patient population specifically in CA. ● The project upholds principles of Diversity, Equity, and Inclusion (DEI). ● DEI was adequately addressed.
No: 1	● No clear statement on how this project will uphold DEI. The overall DEI section needs to be more fully developed with a proactive approach toward upholding principles of DEI.

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	0	*none*
6-8: Responsive	7	• The investigators summarize the racial disparities associated with metastatic breast cancer in terms of early diagnosis, prognosis, morbidity, and mortality. Among patients with breast cancer, Black women are more likely to have metastatic disease compared to Hispanic and non-Hispanic White women. • In addition, the investigators noted that lower economic status, that is often associated with lack of insurance and access to health care, results in these individuals not having access to potentially life saving treatments like HSC transplantation. • The investigators noted that if this approach is successful, it may be applied to conditions that disproportionately impact underserved communities (i.e., sickle cell anemia, SCID). • Upon completion of the TRAN grant, a clinical trial will be initiated in patients with metastatic breast cancer. The investigators will utilize the extensive resources at the applicant institution to recruit a sample of women from under-represented minorities. • A description is provided of the robust DEI initiatives that are in place at the applicant institution(s). • Strong institutional support of DEI. • Very strong track record. • Adequate DEI incorporation for proposed project. • In terms of product development, the investigators will include in their process development, biospecimens from donors of different racial and ethnic groups that are representative of the diversity of California. However, the anticipated proportion of donors from the various ethnic groups was not provided in the grant application.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-15264
Title (as written by the applicant)	CDC42 Inhibitors for the Treatment of Melanoma
Translational Candidate (as written by the applicant)	We have developed a small molecule that inhibits the ability of melanoma tumors to grow and recruit the vessels needed to feed them.
Area of Impact (as written by the applicant)	The drug would be used to treat acral melanoma, a rare subtype that predominantly affects ethnic minority populations.
Mechanism of Action (as written by the applicant)	While many different melanoma treatments have been developed, there are still many patients that cannot tolerate existing medications or develop resistance to them. This is a particular problem in acral melanoma, which is resistant to most therapies. Here we develop a small molecule to treat acral melanoma and melanoma tumors that have developed resistance to existing therapies.
Unmet Medical Need (as written by the applicant)	We develop a treatment for acral melanoma, a rare subtype of melanoma that affects ethnic minority populations that is resistant to existing therapies.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Formulate the compound into a drug and measure its pharmacology, distribution, and toxicity in animal models • Determine which subtypes of melanoma tumors are killed by the drug • Identify biomarkers that could predict which patients would most benefit from this therapy
Statement of Benefit to California (as written by the applicant)	In this proposal, we develop a new treatment for melanoma, a cancer for which current treatments are effective in less than half of patients. In particular, we focus on acral melanoma, a rare subtype of melanoma that is treatment resistant and more common in Asians, African Americans, and Latinos, populations that together comprise a majority of Californians.
Funds Requested	$2,719,482
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: 60

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

Mean	58
Median	60
Standard Deviation	4
Highest	60
Lowest	50
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/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: 6	• The product has the potential to treat acral melanoma, which has a horrible prognosis. • The proposed therapeutic addresses an unmet need, but there are other products in this space. • The product may have some usefulness, but it should be noted that recruitment of other trials in this disease had been slow and trials were terminated. • The stem cell aspect of the proposal is not convincing based on the stated vascular mechanism of action of the small molecule. • The preliminary data indicate that improved survival is comparable to another therapy, vemurafenib.
No: 8	• The proposed agent will have an impact on the management of subtypes of melanoma patients (acral melanoma). However, the investigator's description indicating that the agent will have an effect through arachidonic acid metabolism indicates that this agent may not have a lasting impact on the treatment of acral melanoma. • Clinical targets were not clearly defined and aspects of the project were confusing.
GWG Votes	**Is the rationale sound?**
Yes: 3	• The preliminary data support the rationale. The applicants could consider comparative data to help support the application. • The candidate product selectively inhibits the ability of CDC42 GTPases to activate downstream effectors including a known cancer driver that is one of the most frequent amplifications observed in acral melanoma. • Preliminary data show that the candidate is highly specific for the CDC42 family and does not affect RAC1 GTPases.
No: 11	• The product does not have a stem cell based mechanism. • There is no stem cell involved in the project or the mechanism of the candidate. • The scientific rationale is sound regarding acral melanoma. However, it is not clear how the proposed drug will have a lasting impact on acral melanoma. • The rationale for developing the therapeutic was not well-explained or supported with proof of concept data.
GWG Votes	**Is the project well planned and designed?**
Yes: 2	• The project is well designed.
No: 12	• Commercial viability is a concern. Other programs in acral melanoma were terminated early due to slow enrollment. • The application includes limited preliminary data. • Some of the preliminary data are missing (Figure 9). It is not clear whether human data are available or not. It is not clear whether the investigator has used the candidate in human studies. Proposed investigations are confusing and the design of the animal study could be improved. Specifically, the applicant should use a tumor size of 2 cm as the criteria for euthanasia to determine the late effect of the treatments. The tumor will start showing resistance to the therapies if allowed to grow larger than 1 cm. • Nonclinical proof of concept was sparse and CMC readiness was unclear.
GWG Votes	**Is the project feasible?**
Yes: 7	• The staff are adequate. • The project appears feasible.
No: 7	• The project has a strong dependence on a contractor, and appropriate oversight is critical. • The PI did not state experience with developing drugs and interactions with the FDA. • This is an ambitious project and cannot be finished in the stipulated time. Too many investigations are proposed and the readiness for these studies is questionable. • With inadequately defined clinical targets, the project was not considered feasible.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12	• The primary focus of the work is to develop a treatment for acral melanoma which would specifically address melanoma in African Americans, Asian Americans, and Latinos where existing therapies are ineffective. • The DEI section seems appropriate for this stage of development. • DEI was adequately addressed. • The applicants discuss rarity of the tumor animal models available and a strategy to address this.

	• DEI strategies were very truncated. The application does not address how to ensure recruitment of the patients for the studies in the future. • Target disease is disproportionately found in ethnic/racial minority. However, plan itself is weak
No: 2	• The interpretation of DEI was unclear.

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	5	• In targeting acral melanoma with a small molecule therapy that inhibits tumor growth, this proposal has a strong DEI component because this sub-type of melanoma is relatively rare but when it does occur is most common in Black, Latino and Asian populations. • Because the number of acral cases is quite low, the research will also target this as an adjunctive salvage therapy for individuals whose treatment is not progressing as hoped. Given the populations that would benefit from this therapy, it was surprising that the applicant did not include a more robust discussion of DEI-oriented strategies to be utilized in the research. The applicants do note that gender will be taken into account in the animal studies. • There was adequate DEI incorporation for the proposed project. • It would help to better describe the impact of DEI on product development.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*