APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	DEI SCORE (MEDIAN)	Resubmission	Previous CIRM Funding	Area of Impact
TRAN1-16050	Combating Ovarian Cancer with Stem Cell-Engineered Off-The-Shelf CAR-NKT Cell Therapy	**$6,312,000**	**Y**	**94**	93	2	90	95	14	0	9	N	Y	Project aims to develop an off-the shelf cell therapy for ovarian cancer that could be effective across the diversity of patients.
TRAN1-16225	Development of a universal allogeneic human interneuron cell therapy candidate for the treatment of drug resistant focal epilepsy.	**$3,828,714**	**Y**	**93**	92	4	85	95	13	0	8	N	Y	Project aims to develop a hESC-based therapy for focal epilepsy with universal recipient eligibility.
TRAN1-16011	Development of a Gene Therapy for Treatment of Guanidinoacetate Methyltransferase Deficiency-Translating In Vivo Proof of Concept to Support a Pre-IND	**$5,145,825**	**Y**	**90**	91	1	90	95	13	0	7	N	N	Goal is to develop a gene theray to restore deficiency of the GAMT enzyme in patients.
TRAN1-16026	Toward a Cure for Gaucher Disease Type 1: Autologous Transplantation of Genome Edited Hematopoietic Stem Cells	**$4,997,237**	**Y**	**90**	89	2	85	90	11	0	10	N	Y	Aim is to develop a gene-modified cell therapy that will replace patient blood cells including disease-causing macrophages.
TRAN2-16061	A Rapid Clinical Digital Patient-derived Organoid to Guide Breast Cancer Treatment Decision	**$1,535,375**	**Y**	**90**	88	2	85	90	14	0	8	N	N	Development of a diagnostic test to assess the potential of various treatments in breast cancer patients.
TRAN1-16023	Hypoimmunogenic iPSC-derived TCR-NK cells for oncology	**$4,107,571**	**Y**	**90**	88	8	60	90	13	1	7	N	N	Goal is to develop an NK cell therapy to treat relapsing cancers starting with multiple myeloma.
TRAN1-16012	A high quality, accessible cell therapy for Parkinson's Disease produced in a scalable bioreactor system for 3D cell expansion and differentiation	**$3,999,241**	**Y**	**88**	88	3	84	95	9	3	9	N	Y	Aim is to develop a dopaminergic cell therapy for Parkinson's disease from hESCs using a novel 3D culture system.
TRAN1-16013	Development of an UNC13A Targeting Antisense Oligonucleotide (ASO) Treatment for ALS, for IND-enabling Studies	**$4,012,325**	**Y**	**88**	87	2	83	92	11	2	10	N	N	Goal is to develop an antisense oligonucleotide therapy for ALS that restores the deficient UNC13A protein.
TRAN1-16192	Targeting pancreatic cancer with Allogeneic Off-the-Shelf PSCA-CAR NK cells	**$6,036,000**	**Y**	**88**	87	4	80	93	10	4	6	N	N	Goal is to develop a CAR NK cell therapy targets and treats pancreatic cancer.
TRAN1-16070	Genetic Therapy Targeting mHTT mRNA to Treat Huntington's Disease	**$3,994,237**	**N**	**87**	86	3	80	90	11	3	8	N	N	Aims to develop a small molecule therapy that directly targets the stability of the mHTT mRNA transcript in Huntington's.
TRAN1-16236	A targeted antisense oligonucleotide therapeutic for Timothy syndrome	**$5,944,166**	**N**	**86**	84	5	70	88	9	4	7	Y	N	Develop an antisense oligonucleotide therapy targeting a gene variant in the brain to improve neuropsychiatric symptoms.
TRAN4-16091	Purification of Human Hematopoietic Stem Cells (HSCs) for Clinical Stem Cell Transplantation	**$1,499,683**	**Y**	**85**	86	3	80	90	7	5	8	Y	N	Aims to generate reagents and protocols for HSC purification that provides HSC with the potential to be safer and more effective.
TRAN1-16030	Evaluation of an ex vivo lentiviral gene therapy for the treatment of Angelman syndrome (AS)	**$6,289,988**	**N**	**85**	85	4	75	90	10	3	9	N	N	Goal is to develop a lentiviral gene therapy that restores the Ube3a enzyme missing in Angelman syndrome patients.
TRAN1-16065	A Novel Gene Therapy to Target Glioblastoma via Custom-Engineered Adenovirus-Associated Viral Vectors	**$5,927,453**	**N**	**85**	85	2	80	89	9	4	8	Y	N	Study aims to develop a gene therapy that specifically targets GBM cells and inhibits their survival.
TRAN1-16022	Development of an AAV Epigenetic Gene Therapy for Gain-of-Function SCN9A Disorders and Chronic Pain	**$3,997,149**	**N**	**85**	84	5	70	90	9	5	7	N	Y	Goal is to develop a gene therapy to treat chronic pain.
TRAN1-16262	Parkin Gene Therapy for Parkinson's Disease	**$1,938,990**	**N**	**86**	86	1	85	87	14	0	5	N	N	Aims to develop a gene therapy that restores the Parkin gene in patients with the Parkin-deficient form of PD.
TRAN1-16158	Development of Cargocyte expressing IL-12 for the treatment of metastatic cancers	**$3,196,087**	**N**	**84**	81	5	70	86	6*	7	8	Y	N	Goal is to develop a cell therapy to deliver IL-12 to tumor sites to mediate anti-tumor effects and enable checkpoint inhibitor tx.
TRAN1-16025	Translating iPSC-derived Thymic Epithelial Cells into a Cell Therapy for Children with Congenital Athymia	**$5,880,903**	**N**	**80**	81	3	75	85	1	12	8	N	Y	
TRAN1-16264	Advancing Next Generation CAR-T Cells for Renal Cell Carcinoma	**$4,000,000**	**N**	**80**	78	3	72	85	1	12	7	N	N	

APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	DEI SCORE (MEDIAN)	Resubmission	Previous CIRM Funding	Area of Impact
TRAN1-16217	Targeting triple-negative breast cancer by novel CD4 TCR-engineered T cells	**$3,992,917**	**N**	**78**	76	5	70	83	0	13	8	N	N	
TRAN4-16067	Microfluidic iPSC-derived organoids for high-throughput therapeutic development and drug evaluation	**$1,287,634**	**N**	**75**	74	2	70	77	0	12	9	N	N	
TRAN1-16162	Translation of pan-cancer immunotherapy by GlyTR2 CAR T cells	**$4,598,304**	**N**	**75**	72	7	60	82	0	14	2	N	N	
TRAN2-16130	Organoids Derived from Circulating Cancer Stem Cells for Drug Screening and Longitudinal Non-invasive Monitoring of Cancer Progression	**$1,204,875**	**N**	**68**	65	5	55	70	0	12	7	N	N	
TRAN1-16213	Manufacture and regulatory processing of cone progenitor cells for treating central vision loss	**$2,380,804**	**N**	**65**	66	5	55	75	0	13	7	Y	N	

* Qualify for Minority Report

Application #	TRAN1-16050
Title (as written by the applicant)	Combating Ovarian Cancer with Stem Cell-Engineered Off-The-Shelf CAR-NKT Cell Therapy
Translational Candidate (as written by the applicant)	Stem cell-based off-the-shelf CAR-NKT cells
Area of Impact (as written by the applicant)	Ovarian cancer (OC)
Mechanism of Action (as written by the applicant)	The proposed cell therapy candidate can directly kill OC tumor cells through CAR/NKR dual-targeting mechanisms, and can also modulate OC tumor microenvironment (TME) by depleting immunosuppressive tumor-associated macrophages (TAMs) and myeloid-derived suppressive cells (MDSCs) via iNKT TCR-mediated CD1d recognition. Together, these multi-pronged OC-targeting mechanisms grant the candidate a unique opportunity to combat this hard-to-treat disease.
Unmet Medical Need (as written by the applicant)	OC remains an incurable disease, with a high relapse rate. The proposed therapeutic candidate can offer a new treatment opportunity for the diverse OC patient population.
Project Objective (as written by the applicant)	Pre-IND meeting with the FDA
Major Proposed Activities (as written by the applicant)	• Chemistry/Manufacturing/Control (CMC) study of the therapeutic candidate • Pharmacology study of the therapeutic candidate • Safety study of the therapeutic candidate
Statement of Benefit to California (as written by the applicant)	Ovarian cancer (OC) is the leading cause of death among women with gynecological malignancies. In the USA, California is the state with the highest incidence and deaths from ovarian cancer. In 2023, it is estimated that 2,150 women will be diagnosed with OC and 1,450 women will die from this disease at California. Therefore, novel therapies are urgently needed. The proposed project can potentially lead to a novel off-the-shelf cell therapy for ovarian cancer and save lives.
Funds Requested	$6,312,000
GWG Recommendation	**(85-100): Exceptional merit and warrants funding, if funds are available**
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 94

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	94
Standard Deviation	2
Highest	95
Lowest	90
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 **No:** 0	• Advanced ovarian cancer has limited therapeutic options and a very poor prognosis. • The proposed technology utilizes cord blood-derived hematopoietic stem cells to generate CAR-NKT product. • This "off-the Shelf" stem cell therapy has the potential to be transformative with respect to treating ovarian cancer and presents a high unmet clinical need. The value proposition is likely to be highly impactful based on the data presented in the application. • This is a new submission that builds on a prior CIRM grant to the PI. This proposal would represent a progression from the prior award. In the prior study they have generated CAR-NKT cells characterized for iNKT cell markers and function. Prior reviews of this work note that “progress is steady and the data figures are compelling and a joy to evaluate.” • Personalized autologous CAR T cells are manufactured for each patient and can only be used to treat that single patient, making the therapy extremely costly and difficult to deliver. The development of an allogeneic “off-the-shelf” cell therapy has potential to make CAR-directed cell therapy more widely available and less costly. • The estimated cost of the CAR-NKT cell product is ~$5,000 per dose (per patient per treatment) making it highly cost effective even for financially challenged patients. • The proposed off-the-shelf cell therapy can potentially benefit the diverse OC patient population regardless of age/race/ethnicity/HLA disparities.
GWG Votes	**Is the rationale sound?**
Yes: 12 **No:** 0	• The scientific rationale is sound. • The rationale for this application is supported by data generated by the applicant for a previous application, where a similar type of cells and similar manufacturing technology were used for hematological malignancies. The work was published and licensed. • The scientific rationale behind the intended CMC and nonclinical program is well-considered and carefully planned to meet the intended milestones of the 30-month project culminating in a pre-IND. • The therapeutic candidate mechanism of action is to directly kill OC tumor cells through CAR/NKR dual-targeting. • The selected target is a rational target for ovarian cancer.
GWG Votes	**Is the project well planned and designed?**
Yes: 12 **No:** 0	• The investigators plan to complete the necessary preclinical development activities for a future clinical trial using the CAR-NKT cells to treat ovarian cancer. • Successful completion of the proposed activities will allow for a well-prepared pre-IND meeting with the FDA. • The program is well-written and explained with clear milestones. There has already been considerable effort to demonstrate in vitro and in vitro feasibility, particularly with the development of humanized mouse models that show evidence of tumor regression. Planned studies include dose-range finding, preliminary toxicity assessments, including neurotoxicity, and evaluations of cytokine storm and graft vs. host disease potential. • The panel specifically discussed the importance of the planned studies to assess efficacy and feasibility of the proposed route of administration. Given that CARs can often result in pulmonary toxicities following systemic administration, exploration of local administration is encouraged in direct comparison with systemic, given that not all forms of OC are localized within the peritoneum. Therefore, both routes of administration should be explored further relative to dose, and a deep assessment of off-target toxicity in multiple organs should be evaluated. • In the prior work, the study team established a feeder-free/serum-free CAR-NKT cell culture method that can produce therapeutic levels of pure and potent allogeneic CAR-NKT cells suitable for off-the-shelf cell therapy. • Risks are clearly identified. • Although not part of the current project / proposal, the applicant proposes to administer the product intraperitoneally (IP) in the future clinical trial. Part of the motivation for this is to minimize graft vs. host disease and lung toxicity. There is data that localized CAR-T treatments provide protection against tumor growth at distant, extra-peritoneal sites. For peritoneal predominant disease this makes sense, but some ovarian cancers have predominantly extraperitoneal disease and the proposed route of administration may not be optimal in these patients. Given extraperitoneal responses, it is not clear whether systemic

	toxicities will be minimized using the proposed approach.
GWG Votes	**Is the project feasible?**
Yes: 12 **No:** 0	• Based on the available data presented in the application in conjunction with further planned testing, the milestones set appear to be achievable within the project timeline, taking into account the CMC and nonclinical activities and expertise of the team involved. The project should lead to a pre-IND meeting within the proposed time frame. • In this application, they propose to develop an engineered off-the-shelf cell therapy for ovarian cancer. They will obtain healthy donor cord blood-isolated stem cells from commercial vendors that will be engineered with a lentiviral vector and cultured to develop the cell product. The manufacturing process will take about 6 weeks, and is expected to generate sufficient cells from a single cord blood donor that can be formulated into several thousand doses. • The study team is qualified to perform the proposed studies. They have access to necessary resources to conduct the proposed activities. The team has appropriated contingency plans to manage risks and delays. • The team is well-staffed and qualified to perform the work. • The proposed study is a preparation for an intended phase 1 clinical trial, in which candidate cells will be administered to patients with recurrent OC after a lymphoablative conditioning regimen. The goal of this proposal is to complete a pre-IND package and initiate a pre-IND meeting with the FDA at the end of the Year 2 funding period. Thus, they have not had official correspondence with the FDA yet.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12 **No:** 0	• If successful, the proposed cell therapy will benefit the diverse OC patient population in California and beyond, by providing them with an effective stem cell-based new medicine that is "off-the-shelf', affordable, and available regardless of age, race, ethnicity, and genetic disparities. • All aspects of DEI were appropriately addressed.

DIVERSITY, EQUITY, AND INCLUSION (DEI)

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

DEI Score: 9.0

Up to 7 patient advocate and nurse members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	2	• Well defined DEI plan. • This proposal does an outstanding job of addressing concerns of age, race and ethnicity in finding treatment for ovarian cancer. Key Personnel are assigned very specific duties regarding the enhancement of DEI activities. I would have assigned an even higher score but for my concern about the data from past and on-going studies that show a very low number of Black and Hispanic subjects. Will this happen again despite the efforts described? • In milestones 1-3 the applicant will source diverse donors, and use diverse cell lines in part because Black women seem to have higher genetic risk. In milestone 4 they seek patients with diversity in age, ethnicity and HLA type. They plan to partner with very robust institutional JDEI resources for recruitment and training. • This project would definitely serve a huge unmet need. The outcomes for OC are currently very poor and the inevitable recurrence means travel for multiple treatments. They clearly point out that the outcomes for Black women are worse in terms of the aggressiveness of the illness and the mortality outcomes even when controlling for access to care. With limited access, of course, outcomes are even worse.

		• If successful, this effort would make a cure for OC thereby reducing cost and issues of access. It also could help by providing guidance on the treatment of Black women by considering genetic issues through the use of primary OC cells from diverse populations, • The applicant plans to incorporate the perspectives of women with OC by partnering with an OC patient circle, using clinical trial navigators, and conducting on-line training and workshops.
6-8: Responsive	1	*none*
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-16225
Title (as written by the applicant)	Development of a universal allogeneic human interneuron cell therapy candidate for the treatment of drug resistant focal epilepsy.
Translational Candidate (as written by the applicant)	Development of a universal allogeneic human interneuron cell therapy candidate for the treatment of drug resistant focal epilepsy.
Area of Impact (as written by the applicant)	Non-destructive treatment option for drug-resistant focal epilepsy patients with reduced immunosuppression regimen and universal recipient eligibility
Mechanism of Action (as written by the applicant)	The proposed therapeutic candidate comprises inhibitory interneurons that would be delivered in a one-time procedure into affected region of the brain and is intended to increase local GABAergic inhibitory tone and rebalance neural activity. The proposed candidate represents a cell replacement therapy that could compensate for the loss and dysfunction of the same types of neurons in the epileptic brain and possibly eliminate/significantly reduce seizures.
Unmet Medical Need (as written by the applicant)	Epilepsy ranks as the fourth most common neurological condition in the US. One-third of people with epilepsy are classified as having seizures that are drug-resistant, which can be profoundly disabling and detrimental to their quality of life. Current treatment options do not typically culminate in seizure freedom and/or risk serious adverse events. Hence, there exists a compelling need to develop alternative therapies that are less invasive, non-destructive, safe, effective, and durable.
Project Objective (as written by the applicant)	Pre-IND meeting with the FDA
Major Proposed Activities (as written by the applicant)	• Evaluation of candidate immunogenicity in a variety of human cellular and humanized mouse models. • Development and qualification of analytical assays and manufacturing of pilot universal allogeneic human interneuron cell therapy material. • Pilot Pharmacology, Dose-Finding, and Safety Studies in an established mouse model of temporal lobe epilepsy.
Statement of Benefit to California (as written by the applicant)	Epilepsy affects over 400,000 people in California, one-third of whom have seizures that are drug-resistant, can be disabling, and affect quality of life. A universal allogeneic inhibitory neuron cell therapy candidate will benefit California's diverse population by providing a non-tissue destructive, regenerative treatment alternative for drug resistant focal epilepsy that does not require concurrent immunosuppression and improves safety, accessibility, and clinical utility for all patients.
Funds Requested	$3,828,714
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: 93

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	93
Standard Deviation	4
Highest	95
Lowest	85
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 11 **No:** 0	• Mesial temporal lobe epilepsy (MTLE) is serious (10K new diagnosis per year) with one-third of epilepsy patients are classified as drug-resistant. • More than 3 million people in the US with epilepsy, 1/3 of which can't be controlled by antiseizure medications. These applicants currently have an existing clinical trial that relies on immunosuppression, which is a continuous concern for quality of life and responsible for most of the adverse effects in the current trial. This application plans to use the same cell line that is being used in the existing clinical trial, but with an already generated mutation that that provides immune-cloaking alleviating the need for immunosuppressants. • I liked the novel approach. It is a complex plan trying to understand the immune response but I believe this effort will have a positive impact on the field of cell therapy overall. • Project is focused on treating drug resistant epilepsy and extends an existing clinical trial (funded in part by CIRM). • Normally I would say wait for the results from the next five patients in the active study of the prior product. However, if this modified version is successful, it could benefit cell transplantation across other applications that currently require immunosuppression.
GWG Votes	**Is the rationale sound?**
Yes: 11 **No:** 0	• The strength of this application is the success the applicants are having in the current clinical trial. They have demonstrated that their current trial is successful in reducing seizures but that immunosuppression and the life altering effects of this is a stumbling block. Their plan to shield the transplanted cells from the immune system is well grounded in the scientific literature. • Current trial requires immune suppression which is a major burden for patients. The goal is to advance an immune-cloaked, allogeneic human inhibitory interneuron candidate toward a first clinical trial for the treatment of drug resistant focal epilepsy without immunosuppression. • Expression of HLA has been suggested to be the major culprit thus functional ablation of a subunit of all HLA-I molecules needed for proper folding and cell surface expression of HLA-I seems to be a logical approach. • The editing of the GMP hESC line is already complete and the applicants have demonstrated that it is immunocloaked and functionally the same as the unaltered cell line in research grade assays. • Thorough preliminary data was presented.
GWG Votes	**Is the project well planned and designed?**
Yes: 11 **No:** 0	• They presented a comprehensive preclinical plan: two studies focused on immune response, a model of MTLE, and preliminary safety/tumorgenicity study, all in mouse models. • The candidate will be produced, cryopreserved, and functionally tested using lymphocyte cytotoxicity assays to confirm evasion of allogeneic T, NK, and macrophage/microglial cells in vitro. • The immune-cloaked product will then be tested for immune evasion in two humanized mouse models reconstituted with allogeneic human PBMC and CD34+ HSC cells • Finally, applicant proposes to evaluate multiple doses of the immune-cloaked interneuron candidate for efficacy and safety in a mouse model of chronic mesial temporal lobe epilepsy. • Yes, the plan to produce a therapeutic is sound and the team has demonstrated that they have the experience to achieve this. At a high level the plan includes ensuring the cells are immune-cloaked in a mouse model, developing all the assays needed to qualify manufactured lots of cells, creating and characterizing the cell banks, completing the final functional animal studies and regulatory interaction to achieve clinical trial approval. The team has demonstrated that they have the experience to achieve this. • Applicant already successfully developed a cGMP-compliant product candidate that is currently in an ongoing phase 1/2 clinical trial for chronic drug-resistant unilateral MTLE.

	• Good contingency plan with some alternative methods that might be needed; the company will carry the costs.
GWG Votes	**Is the project feasible?**
Yes: 11 **No:** 0	• The team is highly qualified and experienced given the success of the current clinical trials. • The described in-house lab space is clearly suitable. • The applicants have clearly defined risks and the steps they can take to mitigate the risks, including unexpected mutations in the modified cell line, failure of cell line production run and lack of efficacy of released lot in mouse epilepsy model. • The neuronal candidate does not expand or proliferate post-administration, which reduces safety risk of tumorigenesis or off-target cell fate. • Applicant performed scRNAseq on wild type and modified interneurons pre-transplant, and snRNAseq on isolated human nuclei post-transplantation into immunocompromised mice and confirmed the absence of an extended list of NK activating ligands. • Preliminary data suggesting that introduction of the mutation is sufficient to evade allogeneic T and NK cell recognition by the interneuron product. • Minor caveat: they saw minor level of baseline cytolysis of the product that could not further be reduced. It was not discussed whether this could be an issue.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 11 **No:** 0	• This application describes how they interact with members of the underserved communities enlist their help in educating their own communities on epilepsy and inform of potential treatment options. Using this insight as to how to engage with members of underserved patient populations is the best way to get their communities involved. • Steps are proposed to incorporate underserved populations include covering travel costs to remove socioeconomic barriers and targeting literature to underserved groups. • There is a description of plans to interact and educate members of the underserved communities on epilepsy and inform them of potential treatment options. • Immune-cloaked cells will be suitable for all populations and will not depend on population-specific donors. • The product is a universally applicable therapeutic and provides durable efficacy in a racially diverse population. Sex differences should also not be an issue. • It looks like they are doing well on DEI in the current trial, which sets a good precedent for their future work. • Company continues good practices recognized in their current CIRM-funded program.

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	2	• Builds on current, mostly successful technology. I think an ideal program for CIRM to fund. • Adequate DEI plan.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-16011
Title (as written by the applicant)	Development of a Gene Therapy for Treatment of Guanidinoacetate Methyltransferase Deficiency-Translating In Vivo Proof of Concept to Support a Pre-IND
Translational Candidate (as written by the applicant)	Adeno-associated viral vector serotyped for tropism to express guanidinoacetate methyltransferase in hepatocytes and brain cells.
Area of Impact (as written by the applicant)	Developing a new therapy for Guanidinoacetate Methyltransferase 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 GAMT protein in the cells of those with GAMT deficiency to effectively treat this condition. It will be delivered intravenously & target the liver primarily. Successfully restoring GAMT expression will resolve the elevated guanidinoacetic acid levels and resolve the abnormally low creatine shown to result in abnormal function of the brain of afflicted patients.
Unmet Medical Need (as written by the applicant)	Guanidinoacetate Methyltransferse Deficiency results in intellectual disability, behavioral disturbances, lack of speech, and is often associated with seizures. Therapy today is all dietary which can be effective to restore creatine levels but is often minimally effective at controlling the neurotoxin GAA. 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 GAMT. • 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 Guanidinoacetate Methyltransferase Deficiency, are more common 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 & vendors in our state & country, including the Association for Creatine Deficiencies, for endpoint outcomes. Our efforts will support identification & inclusion of California families in pursuit of a therapy.
Funds Requested	$5,145,825
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	1
Highest	95
Lowest	90
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 11 **No:** 0	• This application proposes a gene therapy approach to treating guanidinoacetate methyltransferase (GAMT) deficiency, in which a metabolite GAA accumulates, resulting in multiple developmental problems that can include intellectual disability, hypotonia, ataxia, autistic or self-aggressive behavior, and often medication refractory seizures. • Current therapy is a life-long treatment with oral high-dose creatine to replenish cerebral creatine, ornithine supplementation with arginine and protein restriction. This therapy is not completely effective, and elevated GAA levels (up to ten times above normal) are common even with optimal therapy. • Even with optimal oral therapy, GAA brain levels may remain 10 times above normal values with persistence of neurological symptoms & seizures. Moreover, the dietary maintenance program can lead to compliance issues. High-dose creatine also can lead to kidney stones and potential liver dysfunction. • GAA neurotoxicity may explain why creatine supplementation alone has only had very limited success in treating GAMT deficiency. • While dietary supplementation with creatine can alleviate some of the clinical manifestations of this metabolic disease, only gene correction therapy offers the likelihood of effective lifelong improvement. • The product has the potential to directly impact an unmet medical need. Current therapies have modest benefit, and while clearly better than no intervention, the impact on patients is significant and devastating. • The product has the potential to directly impact disease progression and provide much needed intervention to patients. • The Recommended Uniform Screening Panel (RUSP) approved GAMT for newborn screening programs nationwide. It is presently included in some state programs; as such, a better understanding of disease mechanisms and improved treatments are timely and needed. • Although inherited, GAMT deficiency is very rare disease, and correction of this genetic defect in these patients will have tremendous clinical impact on their lives, their families and their health care providers.
GWG Votes	**Is the rationale sound?**
Yes: 11 **No:** 0	• The group involved in the program appears to have extensive experience in the disease condition, and most important, clear insight into the fundamental cause of the disease. • The proposed gene therapy approach addresses the unmet treatment in a scientifically and medically appropriate manner. • Gene therapy has the potential to address the root cause and correct the enzyme deficiency. • It is evident throughout the literature, and based on the clinical experience of this team in treating these patients, even suboptimal reduction of plasma GAA can reduce epilepsy and improve patient outcomes, demonstrating the importance of having medical access and effective GAA-lowering management approaches. • The goal of AAV GAMT gene therapy is restoration of normal levels of GAMT enzyme production in hepatocytes. The fact that other genetic metabolic diseases of the liver have been effectively treated with this approach provides strong support for this AAV gene therapy approach. • The proposal is based on sound scientific principle. Gene therapy to the liver has been established in multiple research programs and in clinical trials. • The mouse model of GAMT deficiency is viable and long-lived, and accurately reproduces the biochemical phenotype of GAMT-deficient patients. Thus, the model allows assessment of effects of gene therapy on lowering GAA levels, increasing creatine, and improving behavioral activity and the firing frequency in Purkinje neurons. • The preclinical murine studies with AAV-based gene therapy to restore GAMT expression

	have resulted in normalization of plasma creatine levels & elimination of toxic GAA. This has resulted in normalization of brain activity and metabolism and mouse behavior. ● This therapeutic approach is supported by substantive data showing efficacy of AAV gene therapy in a murine model of this genetic disease. ● Normalization of GAMT expression by AAV promotes marked improvement of systemic and neurologic abnormalities in GAMT-/- mice.
GWG Votes	**Is the project well planned and designed?**
Yes: 11 **No:** 0	● The gene therapy approach proposed would improve upon currently less-than-optimal treatment strategies. If successful in afflicted patients, this gene therapy approach represents a potential sea change in the treatment of this disorder, which has been waiting for a breakthrough for the last 20 years. ● This team has extensive experience clinically with metabolic disorder patients, in research on gene therapy for creatine deficiency disorders, and in performance of pre-clinical studies needed to take AAV-based gene therapy for GAMT deficiency to the clinic. Multiple team members have been working in the area of GAMT deficiency before in all aspects of the project. ● The lead investigator was the site PI for a completed Phase I/II AAV gene therapy for another metabolic disorder and is the site PI for the Phase III trial, for which they have already dosed 1 patient. ● The investigator's lab is uniquely positioned to accomplish the tasks detailed in the milestones within a two- and one-half-year timeframe. This research group has reported the only successful gene therapy of the disorder and its effect on the metabolic activity of the central nervous system and has gained extensive experience in AAV-based gene therapy of several monogenic disorders over the past 20 years. ● Two doctors on the project team are considered to be experts in the clinical management of these patients. An advisor to this program has led CIRM-funded clinical trials in rare disorders. Another team member has stewarded several gene therapy programs for rare disorders toward clinical trials and FDA review. The selected consulting firm has assisted numerous investigators in regulatory filings and INTERACT/IND meetings with the FDA (and EMA). The institution's regulatory officer will provide support. In addition, this work is being performed at a center and by a PI where there are several active clinical trials in gene therapy which will undoubtedly foster the progression of this project to the clinic. ● Proposed studies are well designed and clearly presented. GLP grade AAV vector will be used to carry out studies needed for IND submission. ● Proposed studies include safety as well as efficacy studies, primarily in GAMT-/- mice. ● AAV-GAMT vector will be produced in a GLP scale manufacturing process at the experienced CDMO. The biodistribution, pharmacology, and toxicology of the AAV-GAMT vector will be assessed in wild type mice. Efficacy of the vector will be assessed in GAMT-deficient mice (GAMT-/-). ● The project plan meets all necessary objectives to move the program from the pre-IND stage into the IND-enabling stage. ● The plan outlines potential risks and failure points and addresses possible actions and remedies.
GWG Votes	**Is the project feasible?**
Yes: 11 **No:** 0	● AAV clinical trials for the treatment of Phenylketonuria and Methylmalonic Acidemia are ongoing, and these are also metabolic disorders of the liver. More than 3,000 children world-wide have been treated with the Novartis AAV9 commercial gene therapy product for Spinal Muscular Atrophy (SMA). with relatively few adverse events. ● The viral vector serotype and construct developed for GAMT deficiency as part of this proposal are quite similar to those already in clinical development with an effective dose (in mice) that is substantially lower. The relative efficacy and safety of this approach is quite promising and the track record from both the OTC gene therapy clinical trial and Zolgensma for SMA support the feasibility of using a similar approach to treat another disorder, in this case GAMT defciency. ● This team has extensive experience clinically with metabolic disorder patients, in research on gene therapy for creatine deficiency disorders, and in performance of pre-clinical studies needed to take AAV-based gene therapy for GAMT deficiency to the clinic. ● The proposed team has the appropriate expertise needed for this project. ● The project is feasible and milestones are appropriate. ● Available resources are appropriate for this project. ● The milestones are appropriate and reflect comprehension of reasonable time frames. ● Adequate consideration has been given to potential failure points and means to address and compensate for most changes (short absolute failure in efficacy or tolerability).

GWG Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
Yes: 11 **No:** 0	• The affected population is well represented in the plans for this project and is very supportive. • The relationship of the investigators with the Association of Creatine Deficiencies will ensure access to caregivers for Milestone 4 of this proposal and to patients for an eventual clinical trial. • The group plans to make outreach and attempt to enroll all ethnic groups in a clinical trial. The AAV-based gene therapy is expected to be equally effective in all racial groups and genders; the gene addition approach is broadly universal and with be applicable to all racial groups and all mutations. • As the host institution is a significant source of referral for patients with metabolic disorders, they have in existence a multicultural team with fluency not only in English but also in Spanish and Farsi; their clinical metabolic team includes members with global origins. • The PI has attended meetings of the Association for Creatine Deficiencies, a parent/caregiver/stakeholder group (https://creatineinfo.org/) that supports research in, and development of, new therapies for creatine deficiency disorders. He has interacted with patients with GAMT deficiency and their caregivers. • GAMT deficiency is a very rare genetic disease with no gender bias. • Patients with rare diseases such as metabolic disorders, of which GAMT Deficiency is one, are often cared for in a variety of clinics and hospitals, only some of which are local. Expertise can vary widely, and these differences can be exacerbated in marginalized and low income communities where the most advanced and well-staffed hospital infrastructure may not exist. Traveling to a distant academic medical center, while the expertise is present, can place an undue burden on working parent caregivers and families who already often live at their financial means. • Since this is a rare genetic disease, the product will only address the unmet medical needs of this small population.

DIVERSITY, EQUITY, AND INCLUSION (DEI)

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

DEI Score: 7.0

Up to 7 patient advocate and nurse members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	0	*none*
6-8: Responsive	2	• Very strong DEI track record on patients at the applicant institution. As GMAT is a rare disease, with estimates for a US population of 6 -26 newborns per year. The addition of GMAT to newborn screening panels currently underway has the potential to increase that to 50 per year. • As GAMT Deficiency is not common, in the setting of a clinical trial the applicants have informational sessions with caregivers/candidates who are interested and have a desire to enroll. This will be performed by the active involvement of a partinent parent and stakeholder group. The active involvement of this group is critical. They are a collaborative unit with this proposal as represented by the Executive Director, who is a member of this TRAN team. • Full acknowledgement and awareness of potential complexities related to demographics are well understood, but limited data limits further a priori elements related to product development at this time. • The proposal contains an adequate DEI plan.
3-5: Not fully	0	*none*

responsive		
0-2: Not responsive	0	*none*

Application #	TRAN1-16026
Title (as written by the applicant)	Toward a Cure for Gaucher Disease Type 1: Autologous Transplantation of Genome Edited Hematopoietic Stem Cells
Translational Candidate (as written by the applicant)	Autologous blood stem cells edited to restore glucocerebrosidase expression
Area of Impact (as written by the applicant)	Gaucher disease type 1 (non-neuronopathic)
Mechanism of Action (as written by the applicant)	To treat Gaucher disease, autologous blood stem cells undergo genome editing to restore the deficient enzyme. Reintroducing these edited cells replaces the patient's bone marrow, establishing a lasting enzyme reservoir. The bone marrow produces enzyme-secreting cells, replaces disease macrophages, and generates cells that migrate to affected organs, locally delivering the enzyme and mitigating the disease's visceral and skeletal manifestations.
Unmet Medical Need (as written by the applicant)	Gaucher disease presents in three primary clinical forms, namely types 1 (GD1), 2 (GD2), and 3 (GD3). Current treatments for GD1 require life-long administration, do not eliminate all symptoms, and lower the quality of life due to financial and logistical burdens. Unfortunately, there are no treatments available for GD2 or GD3. gtCCR5-GBA could offer a definitive treatment for all manifestations of GD1 and could also be a promising strategy for GD2 and 3.
Project Objective (as written by the applicant)	Pre-IND meeting with the FDA
Major Proposed Activities (as written by the applicant)	• Establish a GMP-compatible process for patient-scale manufacturing runs and develop the necessary analytical assays to characterize the product • Re-demonstrate efficacy with a GLP-certified study • Prepare for and conduct a pre-IND meeting with the FDA
Statement of Benefit to California (as written by the applicant)	Gaucher type 1 (GD1) is a rare multisystemic genetic disorder for which a cure may be possible. As a populous state, California deals with a significant GD1 patient population. Autologous transplantation using genome-edited cells offers a once-and-done therapy for GD1, providing a unique opportunity for researchers and patients in California to establish a definitive treatment. This approach can reduce long-term healthcare costs and improve the patient's quality of life.
Funds Requested	$4,997,237
GWG Recommendation	**(85-100): Exceptional merit and warrants funding, if funds are available**
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 90

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

Mean	89
Median	90
Standard Deviation	2
Highest	90
Lowest	85
Count	11
(85-100): Exceptional merit and warrants funding, if funds are available	11
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 9 **No:** 0	• The overall project has a significant potential for impact in Gaucher Disease (GD) and in lysosomal storage disorders, more broadly. Also, the platform represents an important innovation in the gene edited HSPC therapy space. • While enzyme replacement therapy is partially effective for GD, the potential for auto-transplant with glucocerebrosidase (GBA)-corrected cells could result in improved outcomes.
GWG Votes	**Is the rationale sound?**
Yes: 9 **No:** 0	• The pre-clinical data are stellar. There are great data and rationale for the overall drug product. • The applicant needs to perform a titration experiment with actual gene modified cells (not wild type). • It's important to note that GBA-modified HSC will have no survival advantage over non-corrected cells. Mixed GBA chimerism is to be expected.
GWG Votes	**Is the project well planned and designed?**
Yes: 9 **No:** 0	• Yes, this is extremely well planned and designed. • Very well done.
GWG Votes	**Is the project feasible?**
Yes: 9 **No:** 0	• The team has a strong network and infrastructure that will enable this project to create significant value for the field. • This is a strong that team will solve any issues that arise.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 9 **No:** 0	• The DEI section is stellar. • Part 1: The applicant provides a thorough description of the incidence, prevalence including the ethnic communities most impacted. • Part 2: The applicant describes the financial burden that results from current therapies. The applicant states that their approach has the potential to address this critical needs and, as a comprehensive therapeutic option with curative potential, offers a substantial advantage over current treatment alternatives. • They recognize that their relationship with the Gaucher Community Alliance and their outreach efforts have an essential role as a vital source of information and support for affected families. They intend to share their progress and findings with affected communities through presentations at events organized by this and another alliances and groups and monthly webinars. They intend to draft a Trial Diversity Plan including defining enrollment goals to ensure representation of ethnicities most affected by Gaucher Disease Type 1 in their patient population. • Part 3: They aim to gather diverse perspectives from individuals who will benefit from their efforts, including insights from patients and collaborations with patient organizations. Their DEI enhancement initiative intends to significantly emphasize educating the GD community about gene therapy in general and their cell product. They particularly focus on reaching those with limited medical or scientific literacy. • Activities intended engage the target population will be carried out with the support of the Gaucher Community Alliance which aims to educate and support patients and families with Gaucher disease through peer-to-peer support and education, advocacy, patient and family resources, and networking. The applicant plans to collaborate with the National Gaucher Foundation which empowers Gaucher patients through financial support, educational programming, patient services, and collaboration with medical professionals. • They intend to implement an advisory panel of key opinion leaders, patient advocates, and our core GD1 team members. They will develop 5th-grade level reading material to explain the GD1 program in multiple languages. Applicant describes their intention to use Stanford's DEI education for providers and others advancing therapeutics.

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: 10.0

Up to 7 patient advocate and nurse members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?

9-10: Outstanding response	1	• The DEI section is stellar.
		  • Part 1: The applicant provides a thorough description of the incidence, prevalence including the ethnic communities most impacted.
		  • Part 2: The applicant describes the financial burden that results from current therapies. The applicant states that their approach has the potential to address this critical issue and, as a comprehensive therapeutic option with curative potential, offers a substantial advantage over current treatment alternatives.
		  • They recognize that their relationships/partnerships with a Gaucher disease community alliance and other groups, and their outreach efforts, have an essential role as a vital source of information and support for affected families. They intend to share their progress and findings with affected communities through presentations at events they name in the proposal and monthly webinars.
		  • They intend to draft a Trial Diversity Plan including defining enrollment goals to ensure representation of ethnicities most affected by Gaucher Disease Type 1 in their patient population.
		  • Part 3: They aim to gather diverse perspectives from individuals who will benefit from the proposed product efforts, including insights from patients and collaborations with patient organizations. Their DEI enhancement initiative intends to significantly emphasize educating the GD community about gene therapy in general and their cell product. They particularly focus on reaching those with limited medical or scientific literacy.
		  • They will develop 5th-grade level reading material to explain the GD1 program in multiple languages.
		  • They will leverage institutional DEI educational offerings for the project team.

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

Application #	TRAN2-16061
Title (as written by the applicant)	A Rapid Clinical Digital Patient-derived Organoid to Guide Breast Cancer Treatment Decision
Translational Candidate (as written by the applicant)	The digital patient organoid (DPO) assay is a microfluidic miniature organoid technology that allows high-throughput drug testing.
Area of Impact (as written by the applicant)	Our functional DPO assay will guide personalized therapy in patients with metastatic breast cancer and fulfill a gap of huge unmet need
Mechanism of Action (as written by the applicant)	DPO is a microfluidic miniature organoid technology that enables breast cancer stem cells to form organoids rapidly in the presence of original tumor stromal and immune cells in droplet-sized (250 uM) balls made of extracellular matrix, which is a high-throughput, high-fidelity patient-derived model for rapid drug testing and maintains the original tumor microenvironment and enable personalized treatment for patients with metastatic cancers.
Unmet Medical Need (as written by the applicant)	Metastatic breast cancer (MBC) remains incurable despite recent incorporation of antibody drug conjugates (ADCs). With the fast-paced clinical development of multiple ADCs in the MBC space, lack of trial data or clinical algorithm guiding subsequent therapy following initial ADC resistance, such as a different ADC or combination. There is urgent need for development of novel precision medicine tool using a reliable and rapid turn-round assay guiding treatment selection in these patients.
Project Objective (as written by the applicant)	Pre-IND
Major Proposed Activities (as written by the applicant)	• To assess the DPO platform's ability to predict patient treatment response to therapy in a prospective clinical study • To conduct high-throughput screening to identify individualized recommendations of therapy for ADC-mediated drug resistance • To understand the molecular mechanism of ADC resistance to T-DXd and SG.
Statement of Benefit to California (as written by the applicant)	Metastatic breast cancer (MBC) remains incurable and 2nd leading cause of cancer death in women in California. The precision medicine treatment for MBC is hindered by lack of functional tools predicting drug sensitivity. Our tool enables high throughput drug testing for faster and more effective identification of therapeutic agents or combination for treatment of MBC, an enormous benefit for the healthcare of Californians.
Funds Requested	$1,535,375
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	88
Median	90
Standard Deviation	2
Highest	90
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 **No:** 0	• In the current standard-of-care setting, oncologists prescribe next line of therapy without patient-specific guidance; they use guidelines, pathological/genomic features of disease, and prior treatment history. Digital patient organoid (DPO)-guided cancer treatment would offer the benefit of minimizing excessive/unwanted toxicities by choosing the most effective treatment, minimizing the use of ineffective agents, and offering the possibility of de-escalation, hence improving patients' survival and quality of life. • The identification of a means to guide therapy after ADC treatment is an unmet clinical need. In vitro methods to identify treatment resistance have largely lacked strong clinical correlation. The focus on ADC is interesting, as resistance may come about due to changes in the molecular target and/or the cytotoxic payload. • As the number of validated drug targets – and FDA-approved and experimental cancer therapies against those targets – grows, oncology needs next-generation precision medicine strategies that complement molecular profiling with rapid functional drug testing to increase predictive power. • The proposed product could improve current therapy and prediction of response.
GWG Votes	**Is the rationale sound?**
Yes: 12 **No:** 0	• The foundation of the proposed functional breast cancer assay is based on the cell killing efficacy of a drug or combination therapy on DPO derived from a patient's breast tumor biopsy. This technology has already been used in a clinical trial in colorectal cancer and been used by other pharmaceutical companies. It has shown to be predictive of chemo/targeted/immunotherapy response. • The proposed DPO technology outperforms current patient-derived cancer models for clinical application due to its speed, high success rate with small biopsies, and re-capitulation of the tumor immune microenvironment. DPO is a high throughput platform for testing drug combinations with excellent reproducibility as the entire process is automated. • The applicant has carried out histopathological assessment of their DPO models to determine how closely they resemble the original patient tumor. • Models were assessed by two blinded pathologists who found the majority to contain an estimated 80-90% BC cells. Phenotypic consistencies with cancer types were also reported, verifying that the models morphologically resemble their original tumor counterparts. • Demonstration of the translation of this technology is evidenced by a registered, multi-center trial led by two institutions to test the DPO assay for guiding colorectal cancer standard-of-care treatment. • They have conducted comprehensive characterization of DPO for multiple cancer types. The relative proportion of all cell types, including immune cells and fibroblasts, were conserved between tissue and DPO samples. The presence of the various TME compartments was also demonstrated using imaging. • The data obtained in their multi-omic analyses will provide strong foundation for Aim 2B. • The proposal includes extensive background data on in vitro DPO organelle studies. • The available data support development of this product.
GWG Votes	**Is the project well planned and designed?**
Yes: 12 **No:** 0	• They have developed an optimized workflow that efficiently moves tissue samples to DPO to dosing studies. These efforts included exploring different media formulations, cell isolation approaches, and incorporation of automation and high-throughput imaging. Automated fluid handlers were used for drug studies, to reduce human-error and bias. They designed a 384-well drug plate to include several standard-of-care chemotherapies broadly prescribed

	across all subtypes of MBC, per consultation with breast oncologists. Each drug was dosed across multiple concentrations in technical replicates and included appropriate negative (vehicle and untreated) and positive controls. They rigorously verified the reproducibility of their drug assay by dosing three separate breast DPO lines in technical triplicate over biological triplicate. Their dosing assay showed high reproducibility with excellent signal-to-noise. ● They successfully processed samples, established cultures, and completed dose response studies for all breast cancer models within a median time of around three weeks. ● In a proof-of-concept study, they screened patients' DPO avatars against a few hundred drugs from a thousand past clinical trials at multiple titrations in less than two weeks, which reproduced reported successes and failures of drug candidates from previous clinical trials and showed clinical correlations of approved drugs. Relative dose response curves highlights that many "failed" drugs could have been effective if it was known how to select patients who are responders. ● The ability to identify testing results within 10-14 days is critical in the setting of progressing metastatic disease. ● In Aim 2B, the applicants will explore the mechanisms of ADC resistance by comparing DPO responses with genomic, transcriptomic, and tumor microenvironment analyses. The investigators propose to use the institution's biobank - but the ability to have sequential, longitudinal specimens even from motivated patients is limited. ● The crossover design in Figure 12 is not well described and may not be feasible as eligibility for T-DXd and SG differ. ● Examining different cell ratios, examining biopsies from different tumor regions and different metastases in the same patient, and examining whether whether increasing the number of DPOs analyzed per patient provide qualitatively different outcomes and are all valid and important concerns. ● The study team members have not been in touch with FDA specifically regarding this trial, but provided some information from prior FDA communications regarding the colorectal trial using this technology.
GWG Votes	**Is the project feasible?**
Yes: 12 **No:** 0	● The PI has a strong background in basic sciences, clinical oncology, and translational medicine with specific interest in triple negative breast cancer (TNBC) chemotherapy resistance and novel therapeutics. A breast medical oncologist with a background in translational research for breast cancer will provide clinical review and eligibility screening. A professor in cancer biology with a research focus on carcinogenesis of prostate and breast cancer and wet-lab cell and molecular biology approaches with dry-lab bioinformatic analyses will bring expertise in genomic and bioinformatic analysis for this project. The Scientific Director of the collaborating biobank will provide the biobank and data infrastructure for the project. ● This technology has been deployed in a colon cancer trial although data from that trial is not presented. There is indication of interest from the pharmaceutical industry for use of the approach. ● The cost and limitations of a bespoke, personalized system may challenge the feasibility of this technology.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12 **No:** 0	● The applicant institution's catchment area (for breast cancer) comprises 20% Hispanic, 8% Black and 16.5% API. Clinical trial participation has comprised Hispanic 17.8%, African American/Black 5.5%, and Asian 8.5%. ● The investigators propose to compare genomic features of T-DXd and sacituzumab govitecan resistance in Hispanic, Black, Asian and Non-Hispanic White populations with breast cancer. ● The investigators propose studies comparing toxicities and tolerance of ADCs in in Hispanic, Black, Asian and Non-Hispanic White population with breast cancer.

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	2	• Well defined DEI plan. • This project would use the diverse populations of institution's catchment area to explore a way of finding the best treatment options for refractory metastatic breast cancer. One of the project co-investigator's is an award winner for increasing diversity in breast cancer trials. • The discussion made a point of highlighting the rather consistent lack of Black and Hispanic participation in cancer treatment trials. From the data, they gleaned that 83.4% of trial participants where demographic data were kept were Non-Hispanic Whites. Similarly, for trials that lead to the approval of cancer treatment drugs, only 4% of the participants were black and 5% Hispanic. They cited the obvious barriers of access, cost, transportation, time, cultural attitudes, language, and socioeconomic status. • The applicant reports a significant under representation of Black and Hispanic subjects in meta-analysis of cancer trials. They also discuss differences in response and complications for different groups for different cancers. • The project would improve treatment selection and efficacy for breast cancer ADCs. Their DPO model promises improved success, fast turnaround, lower cost and the promise of expanding the limited data on minorities. Refractory breast cancer is not well treated, they observe, in Hispanic and Black populations. They believe their project would improve on this. • They plan to utilize institutional resources including centers for health equity in cancer research and trials equity and a BC patient group. The applicant details their planned meeting schedule with each of these groups rather than merely referring to them.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-16023
Title (as written by the applicant)	Hypoimmunogenic iPSC-derived TCR-NK cells for oncology
Translational Candidate (as written by the applicant)	iPSC-derived NY-ESO-1 TCR/IL-15 NK cells
Area of Impact (as written by the applicant)	NK drug product homogeneity and engraftment/response durability will be improved by this hypoimmunogenic iPSC-TCR-NK therapy in cancer patients
Mechanism of Action (as written by the applicant)	The MoA of the candidate involves engagement of NY-ESO-1-peptide-presented HLA-A*02 molecules on the surface of tumor cells in tissues by the NY-ESO-1-specific TCR on the iPSC-TCR-NK cells, NK activation, lysis & subsequent killing of tumor cells, and extension of patient life. The low levels of secreted IL-15 from the iPSC-TCR-NK cell also promote in vivo expansion, persistence, and tumor remodeling towards a more immune effector cell permissive microenvironment.
Unmet Medical Need (as written by the applicant)	While great strides have been made in the treatment of multiple myeloma (MM), there are no options for patients who have progressed on B cell maturation antigen-directed therapies. The outcome of relapsed/refractory MM, especially the triple-class refractory MM patients, (refractory to proteasome inhibitor, immunomodulatory drug, and anti-CD38 monoclonal) is dismal. They have an overall response rate of approx 30% and a median PFS of 3-6 months. Our therapy provides a necessary alternative for these patients.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• GMP Activities - GMP edited iPSC generation, Master Cell Banking, GMP iPSC-TCR-NK drug product manufacturing • Animal studies (efficacy & pilot safety) & in vitro hypoimmunogenicity testing of GMP product with immune cells from donors from diverse populations • Pre-IND Meeting
Statement of Benefit to California (as written by the applicant)	This project will provide immediate benefit to the state by contributing to the employment & retention of skilled scientists, technicians, and engineers in California. In the medium term the project will attract funding through investment and partnerships to California contributing to the research economy. Long term, this project will transform patient care to a diverse population by enabling increased access to cancer cell therapies close to home.
Funds Requested	$4,107,571
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	88
Median	90
Standard Deviation	8
Highest	90
Lowest	60
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	1

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 13 **No:** 0	• The technology has multiple advantages compared to currently used therapeutic agents (including CAR-Ts), but estimating an impact on patients and health care is speculative at this stage of development. It is not clear how the proposed product will be able to compete with marketed and highly effective therapies for multiple myeloma (MM) such as CAR-T. • Large unmet clinical need. • The patient population they aim to target initially are relapsed/refractory MM patients who have failed at least 3-4 lines of therapy that align with a certain HLA and antigen-expressing profile. They are targeting patients with advanced disease who may have even failed BCMA-CAR T or bispecific engagers. • The value proposition of this particular approach is presumed to be that this project would create a truly universal, less heterogeneous, re-dosable cell therapy. • The applicant very clearly discusses that because of the expected enhanced safety profile, they anticipate this product will be able to be administered at community clinics and will not require in-patient hospitalization or treatment at large, tertiary treatment centers. The ability to administer this therapy in an outpatient setting will greatly increase its availability to otherwise underserved populations. • There is a need for new therapies for MM. • The proposed iPSC-TCR-NK cell therapy product would increase the likelihood of successfully developing a stem cell technology that significantly improves patient care. As an allogeneic product, many patients will be treated at affordable cost from single bath of product as compared to autologous cell therapy products that are patient-specific. • If the focus is MM, it's unclear how many patients will meet inclusion criteria (the candidate is for failures after all other therapies have been tried).
GWG Votes	**Is the rationale sound?**
Yes: 12 **No:** 1	• The scientific rationale is solid. • Robust rationale. • Yes. CAR-NK therapies (off-the-shelf UCB-derived) have been safe and effective. The investigators build upon theirs and others' experiences. • Preliminary data from their partners have shown that CB-derived NY-ESO-1 TCR/IL-15 NK cells are safe, show superior tumor control and significant improvement in their survival compared to the control mice groups, show better engraftment in the animal's organs and continued persistence in the peripheral blood compared to control groups. • The data presented within this application support development of a genome edited iPSC line using the GMP iPSC line (research iPSC bank). • From the CMC development perspective, the project is scientifically sound and further development of the product is supported by preliminary data provided in the application. • It is not clear if the choice of the target NY-ESO-1 has an advantage over other well-described targets in MM, such as BCMA and GPRC5D (or a combination of these two). No evidence supports that NY-ESO-targeted therapies will be more durable (have fewer relapses) than FDA-approved BCMA-targeted therapies (such as Carvykti or Abecma). • It will be good to have data for cell expansion methodology.
GWG Votes	**Is the project well planned and designed?**
Yes: 13 **No:** 0	• The project is well-planned. • Assays, methods and tests planned to show reproducible disease-modifying activity of the product are well-described and appear appropriate: these include flow cytometry to characterize the phenotype of the drug product candidate (hypoimmune iPSC-TCR-NK cells) including anti-tumor activity that was not specific to the TCR. • The CMC milestones are well detailed and clearly defined. The timing for seeking regulatory advices, including the proposed data package to support meetings with regulatory authorities, is reasonable and acceptable.
GWG Votes	**Is the project feasible?**

Yes: 13 **No:** 0	• The proposed milestones are reasonable. • The majority of the work will be outsourced to CDMOs/CROs - the applicant must qualify these vendors to ensure the quality of the work. • Contingency and risk mitigation are well described. • Timelines are appropriate; team and resources all adequate. • The team is equipped to carry out the project. Feasibility is further supported by the investigators' prior experience in the IND process for a related project. • The milestones and timeline are feasible and very detailed, broken down by primary activities with appropriate deliverables, alternative approaches and risk mitigation strategies. • From the CMC development plan provided in the application, the project seems feasible.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12 **No:** 1	• Diversity is taken into account in the project planning, and the different activities to address diversity are well detailed. • DEI-oriented plans are adequate for the stage of development. • The applicant clearly discusses the disproportionate impact of MM in African American (AA), Hispanic, and immigrant populations. They discuss younger AA/Hispanic populations related to MGUS and impact of SDOH on treatment seeking. They clearly discuss decreased access of URM populations to CAR T and other novel therapies. • The applicant discusses their efforts to ensure their iPSC TCR-NK product can be used as a universal treatment across the population, including building an internal biobank. • The applicant discusses future use of Patient Advocacy and/or specialist DEI consultant.

DIVERSITY, EQUITY, AND INCLUSION (DEI)

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

DEI Score: 7.0

Up to 7 patient advocate and nurse members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	0	*none*
6-8: Responsive	1	• Adequate DEI plan, see below for details. • The applicant states that the lack of need for HLA-matching, other than the TCR-restriction, will increase equity of access to as broad a patient population as possible. They state that If this therapy is successful, a low-price structure will be sought to increase equity of access. • Part 1: The applicant provided an informative table describing the incidence, prevalence and 5-year survival rates among different ethnicities. The applicant describes the challenges of access to care, including access to qualified health care providers and the affordability of care. • Part 2: The current biobank has samples from about 10 donors and will increase to roughly 40 through the purchase of primary immune cells from new donors that will be specifically chosen to represent African American, Hispanic, and Asian populations. Immune cells from the diverse donors will be extensively phenotyped and compared/correlated for levels of protection. • Part 3: The applicant states that the first two years are focused on the clinical manufacturing and validation of the drug product. Thus, they will not have proactively started community engagement activities. However, they plan to begin working with Patient Advocacy and/or DEI consultants from Q7 which will be at the mid-point of the project. Planned activities to undertake in Year 3 (Q7 & 8) in preparation for eventual IND filing include:

		• Engaging with California patient advocacy groups. • Facilitating consumer engagement opportunities to understand public acceptability associated with process for clinical administration of cell therapy, willingness to travel for care, ethical or religious concerns. • Working with patient advocacy groups and clinical trial sites to undertake needs analysis for patient educational materials.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-16012
Title (as written by the applicant)	A high quality, accessible cell therapy for Parkinson's Disease produced in a scalable bioreactor system for 3D cell expansion and differentiation
Translational Candidate (as written by the applicant)	Human pluripotent stem cell expanded and differentiated dopaminergic precursor cells to treat Parkinson's Disease at high quantity and high quality
Area of Impact (as written by the applicant)	This candidate uses a 3D cell culture technology that addresses the manufacturing bottleneck and creates a high-quality scalable cell therapy.
Mechanism of Action (as written by the applicant)	Dopamine producing cells are implanted into the striatum to replace the lost dopaminergic neurons in these patients.
Unmet Medical Need (as written by the applicant)	The current standard of care is L-DOPA, an oral medication that reduces the symptoms caused by Parkinson's Disease. For many patients, this therapy loses its effectiveness over time and the symptoms of Parkinson's increase in severity.
Project Objective (as written by the applicant)	Pre-IND meeting and ready for GMP manufacturing
Major Proposed Activities (as written by the applicant)	• Produce material for 3D cell culture as well as cell banks at scale to support non-clinical animal studies and future clinical translation • Produce dopaminergic neuron precursor cells in a 3D system for animal studies, compatible with the scale needed to meet patients demand • Conduct non-clinical animal studies to define dose ranges and safety profile of the dopaminergic cells produced in the scalable 3D platform
Statement of Benefit to California (as written by the applicant)	The proposed program will develop a scalable manufacturing process to generate high quality dopamine producing cells with high survival and innervation capabilities post-transplantation, for the future implantation of these cells into patients suffering from PD. The ability to scale the process will lower the cost of manufacturing compared to standard methodologies leading to greater product accessibility to meet the large demand in California for these life-changing therapies.
Funds Requested	$3,999,241
GWG Recommendation	**(85-100): Exceptional merit and warrants funding, if funds are available**
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 88

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

Mean	88
Median	88
Standard Deviation	3
Highest	95
Lowest	84
Count	12
(85-100): Exceptional merit and warrants funding, if funds are available	9
(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 **No:** 0	• The proposal aims to develop a cell replacement therapy for Parkinson's Disease (PD), a disease for which there are no cures or regenerative therapies today. Thus, the therapy meets an urgent unmet need. • The applicant's proposal is to develop a 3D manufacturing strategy for dopaminergic neurons that has yielded several fold higher cells than conventional methods and disease modifying activity in a rat model of PD, is therefore a critically important project that needs to be pursued. • The proposed product has the potential to treat PD and is a high-value proposition. One of the main limitations in developing effective therapeutics for PD is limited dopaminergic cells for transplantation within the substantia nigra. The scalable 3D hydrogel technology proposed has the potential to produce scalable, high quality dopaminergic cells to meet clinical demand. The stem cells are sourced from tissue sources which have previously been used in PD cell therapies. • Despite the rapid rate of recent progress in the stem cell field and increasing efforts to translate these into clinical trials, there remain critical roadblocks. The current manufacturing strategies for cell therapies are constrained in production scale by monolayer, 2D-Matrigel based cell culture as well as the very low survival rate of made neurons post-transplantation. This presents a significant problem in current delivery strategies for dopaminergic neuron transplantation therapy. • Yes, the applicant's successful demonstration that the cell cultivation platform can be scaled up to a 1-liter bioreactor and produce midbrain dopaminergic neurons that correct motor deficits in a rat model of Parkinson's disease is an exciting milestone in translating dopaminergic neurons to the clinic. • This is an exciting project that this 3D culture method may solve the urgent needs of large scale, high quality, and better engraftment dopaminergic cell therapy and provide the treatment for many PD patients. • The product has the potential to do this, but based on the data submitted it is unclear if if will.
GWG Votes	**Is the rationale sound?**
Yes: 11 **No:** 0	• There are severe limitations of conventional cell therapy approach for PD, including the lower yields and poor recovery post-cryopreservation and transplant engraftment. There is an urgent need to produce cells with higher engraftment capabilities at large scale using scalable platforms at reduced cost that could support further commercialization, maximizing access to high quality cell therapies for all patients. • The project is well based in literature and therapeutic space with good rationale. The need for increased cell survival has sound rationale. The impact of a few weeks earlier maturation is less valuable. • The properties of the 3D hydrogel enable dopaminergic cells to be released from solid state culture conditions to liquid state without the use of harsh enzymes, thus enabling scalable high quality cells to be produced. • Cell characterization studies showed that the cells produced were of a high quality; gene expression of functional genes typical of dopaminergic cells and disease-modifying genes were preserved within the culture conditions, indicating a high-quality cell-product. • The applicant has developed a culture system which is fully defined and supports scalable 3D cell manufacturing. • Data showed the derived cells exhibited better viability, gene expression profile, and more neurites of higher complexity and longer maximum length compared to cells harvested from 2D. Dopaminergic cells produced in the bioreactor show early onset of disease alleviation in a gold standard rodent model of Parkinsonism, reversing motor symptoms by about four months, with a trend towards an early onset of symptom alleviation by about two months post grafting. • The rationale is partially supported by data. However, it should be recognized that speed of functional recovery is to a large part dependent on tyrosine hydroxylase (TH) content which has not been normalized. • The data presented that shows benefit of the culture system plus cells is not sufficient to support product development at this stage. The applicants would need to show more comparative data in vivo (other cells types present in graft, midbrain identity of DA neurons), report significant and meaningful increase in TH content and quantitative innervation assays after 20 weeks or more, ideally after intranigral graft placement.

GWG Votes	Is the project well planned and designed?
Yes: 11 **No:** 0	• The project is well constructed both in terms of CMC and clinical development. • The development plans appear technically sound with a path to pre-IND. • The proposal includes including establishment of GMP Master and Working Cell Banks and further non-clinical in vivo studies, and then they aim to develop a clinical plan and protocol and prepare documentation for pre-IND meeting. • It is well-constructed. • Unclear why the proposed cell line is used. There are better GMP lines available today.
GWG Votes	**Is the project feasible?**
Yes: 11 **No:** 0	• The mDA cells produced appear to be high quality. The proof-of-concept data in the SD rat PD model show reduction of symptoms and reversal of PD symptoms by 16 weeks post transplantation. Discussion around the longevity and potency of effect indicates longer time points may be needed and an extrapolation of dose. This could be included as further feasibility within the nonclinical testing strategy. • The project is based upon the innovative technologies and strong leadership team. The data of 3D cultured dopaminergic cells are promising. The milestones in this proposal, if successfully executed, could bring dopaminergic neurons closer to the clinic. • Strong leadership, and the team appropriately qualified and staffed. • The timeline is very optimistic and in some cases bordering on unfeasible. As it is now, no delays at all can be had and the in vivo dose finding study is not feasible to conduct within the timeframe. • A better plan for managing delays would be good.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 11 **No:** 0	• The applicant is committed to appropriate representativeness in PD clinical trials. This will not only promote diversity and inclusiveness but will also ensure that the product is tested in a representative population for Parkinson's disease. • This was adequately addressed within the application.

DIVERSITY, EQUITY, AND INCLUSION (DEI)

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

DEI Score: 9.0

Up to 7 patient advocate and nurse members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	2	• The applicant has identified appropriate patients profiles including underserved patients. They describe how they will engage these potential trial participants. • Yes. The future trial will be a first-in-human experiment. A lot will be learned. Two very important issues for further development are the potential for an unwanted immune response to the graft, and insufficient or inappropriate activity of the therapy. • Adequate DEI plan.
6-8: Responsive	0	*none*
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-16013
Title (as written by the applicant)	Development of an UNC13A Targeting Antisense Oligonucleotide (ASO) Treatment for ALS, for IND-enabling Studies
Translational Candidate (as written by the applicant)	An ASO targeting UNC13A
Area of Impact (as written by the applicant)	Amyotrophic Lateral Sclerosis
Mechanism of Action (as written by the applicant)	The ASO targets the cryptic exon (CE) of UNC13A and suppresses CE inclusion during RNA splicing, inhibits nonsense-mediated decay, and increases full length mRNA and protein levels
Unmet Medical Need (as written by the applicant)	To date, therapeutic options for ALS have been limited, and disease-modifying drugs remain to be developed. Current FDA approved drugs Riluzole and edaravone are not effective. Tofersen only targets 2% of ALS patients with SOD1 mutation.
Project Objective (as written by the applicant)	Conduct a pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Develop ASO manufacturing schema and manufacture a non GMP batch of 200g • Conduct pharmacological studies in rodents and another relevant preclinical model • Conduct pilot safety and dose range finding studies in rodents and another relevant preclinical model
Statement of Benefit to California (as written by the applicant)	Being one of the most popular States, California has many ALS patients. We have met many of them during the annual ALS walk. Most of them suffer ALS from unknown causes with only a small percentage have known genetic mutation. The candidate ASO is designed to help more than 97% ALS patients (the percentage of patients with TDP-43 pathology). Our preliminary data showed that it is safe and likely to be effective. This proposal would help us to conduct a successful IND meeting with the FDA.
Funds Requested	$4,012,325
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	2
Highest	92
Lowest	83
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	11
(1-84): Not recommended for funding	2

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 11 **No:** 0	• ALS is a devastating motor neuron disease associated with progressive muscle weakness, eventually leading to paralysis, and difficulty swallowing and breathing. Patients with ALS receive palliative care, including ventilatory support and tracheostomy, walkers or wheelchairs, physical therapy, occupational therapy, speech therapy, nutritional support, as well as psychological and social support. Symptom management is also required to alleviate pain, depression, fatigue, swallowing difficulties, or spasticity and muscle cramps. ALS is age related, with the highest rate of onset between 55 and 75 years. The average survival time after symptom onset is 2-5 years. The estimated incidence by the CDC National ALS Registry is about 24,800 in the United States in 2017. • To date, therapeutic options for ALS have been limited, and disease-modifying drugs remain to be developed. Riluzole, approved by FDA in 1995, provides 2 to 3 months of survival benefit without showing any effect on muscle strength and neurodegeneration. Edaravone, also FDA-approved, demonstrated enhancements in the ALS Functional Rating Scale – Revised (ALSFRS-R), encompassing various functions such as fine motor skills, gross motor abilities, bulbar function, and respiratory capacity in ALS patients. However, these studies were confined to early-stage patients, and the impact on overall survival is unknown. More recently, REVYRIO™ (sodium phenylbutyrate and ursodoxicoltaurine), was approved despite showing only modest effects, and a phase 3 confirmatory trial recently failed, leading to potential withdrawal. Tofersen, recently approved as an antisense oligonucleotide targeting the mutant SOD1 gene, benefits only about 2% of ALS patients possessing the SOD1 mutation. • Thus, there is a pressing need for new therapeutic strategies that rescue multiple forms of ALS, particularly those with unknown genetic etiologies that include approximately 90% of ALS patients. • Since there are currently minimal treatment options for this terrible disease, and strong genome wide association studies (GWAS) associations for the target, it makes a lot of sense to target the UNC13A pathway. • The proposed product has a strong likelihood of impacting a major unmet medical need. ALS is a devastating neurodegenerative disorder with a survival typically between 2-5 years. While not high in prevalence, there is still a high lifelong risk of this disease estimated as 1:400 in the general population with males more frequently affected than females. Currently there are a small number of FDA approved medications for ALS, but NONE of these has significant efficacy in terms of survival. Note that one of the most recently approved drugs, RELYVRIO, was approved contingent on completing a phase 3 trial. This trial just completed and showed no efficacy of the drug, which is likely to be withdrawn. Thus development of a therapy that could significantly increase survival in ALS is desperately needed. • At this point, the eventual cost of the product candidate, should it be approved is unclear, but given the enormous costs incurred in caring for patients with ALS and the poor long term survival, the development costs for this product certainly offer a strong value proposition.
GWG Votes	**Is the rationale sound?**
Yes: 11 **No:** 0	• The rationale for development of the product candidate is well supported by the available data. Importantly, there are already examples of successful ASO drug for a neurodegenerative disease, spinal muscular atrophy. • UNC13A, the target of these studies, was identified as one of the top risk factors in several large scale GWAS studies using sporadic ALS patient samples. UNC13A and its UNC13 protein family are presynaptic proteins found in central and neuromuscular synapses that regulate the release of neurotransmitters, peptides and hormones. In mice, Munc13-1 is required for synaptic vesicle priming; mice lacking Munc13-1 cryptic exons (CE) have disrupted glutamatergic neurotransmission resulting from arrested synaptic vesicle maturation. • Cytoplasmic aggregation and nuclear depletion of TAR DNA-binding protein 43 (TDP-43) is a pathological feature in more than 97% of ALS cases and 45% of FTD cases. Research from other labs show that depletion of TDP-43 in iPSC derived neurons results in inclusion of CE and nonsense mediated decay of mRNAs of several genes including AGRN, RAP1GAP, PFKP, STMN2 and UNC13A. • Of these TDP-43 targets, only UNC13A was identified as an ALS-FTD risk gene in several large scale GWAS studies. These findings validate UNC13A as a target for ALS not only for patients with UNC13A risk alleles, but all patients that exhibit TDP-43 pathology.

	• The applicants have established patient-specific ALS and FTD disease models of both genetically defined and sporadic patients for whom they confirmed the existence of UNC13A risk alleles. They have extensive experience in transcription factor mediated reprogramming of patient iPSCs to form mature neurons in 2D and 3D organoid cultures. These neurons induced from genetically defined and sporadic ALS patients' iPSCs (iNs) robustly recapitulate key ALS/FTD processes including neurodegeneration, dipeptide repeat aggregates (for C9orf72 ALS only), TDP-43 mislocalization, UNC13A CE inclusion and defects in synaptic transmission. • Analysis of UNC13A CE inclusion in bulk RNA-seq data from brain and spinal cord tissues of 377 ALS and FTD patients and controls, showed that the UNC13A CE was detected in post-mortem tissues from patients with TDP-43 pathology, but not from patients who lacked TDP-43 pathology. CE expression mirrored the known tissue distribution of TDP-43 aggregation and clearance: it was specific to ALS spinal cord and motor cortex as well as FTD frontal and temporal cortices, but was absent from the cerebellum in both disease and control tissues. Hyperphosphorylated TDP-43 (pTDP-43) is a key feature of these diseases, and there is a strong association between higher levels of pTDP-43 and higher levels of CE expression in these patient tissues38. Importantly, this analysis showed that ALS and FTD patients without the risk SNPs also have CE inclusion and this is highly correlated with TDP-43 pathology. Further studies (Figure 2d in Brown et al) show that inclusion of CE leads to nonsense-mediated decay (NMD) of UNC13A mRNA and leads to loss of UNC13A protein and function. • Antisense oligonucleotides (ASOs) are an attractive approach for targeting UNC13A CE inclusion in the central nervous system (CNS) because they can be injected directly into the spinal cord, specifically target and block the CE splicing sites on the pre-mRNA,and are less likely to cause peripheral toxicity. ASOs are emerging as a new generation of effective therapies for neurodegenerative diseases such as Duchenne muscular dystrophy, spinal muscular atrophy (SMA) and ALS. Indeed the remarkable therapeutic effects of the exon-skipping ASO nusinersen SMA suggest the possibility of using a similar approach for the UNC13A CE. • The proposed project is based on a strong scientific rationale. An estimated 97% of ALS subjects show mislocalization of the key RNA binding protein TDP-43 which has been shown to cause aberrant mRNA splicing (CE inclusion) of several genes, most importantly UNC13A, a protein that is vital for normal synaptic transmission. The result of this pathophysiology is a significant decrease in UNC13A protein leading to eventual neurodegeneration. Genetic studies have shown that UNC13A polymorphisms lead to increased susceptibility to cryptic exon inclusion in subjects with sporadic ALS (the most common form of the disease). • While there are clearly difficulties in developing good models of ALS for testing drugs such as ASO, the applicants use "humanized" mouse models that recapitulate the UNC13A CE inclusion pathophysiology and also use neurons differentiated from ALS subject derived iPSCs. With these models they are able to show convincing data that the candidate increases UNC13A protein and improves synaptic transmission. • The applicants argue that the candidate targeting UNC13A CE inclusion should be a relevant therapy for the majority of subjects with sporadic ALS. There is however, considerable genetic complexity to sporadic ALS, so the precise population that could benefit if the drug is effective is not totally clear. Nonetheless, even if the eventual target population is only a subset of all sporadic ALS, the major unmet medical need for a truly effective prescription would still well justify supporting development of this candidate. • A panelist expressed concern whether targeting a single molecular pathway in a complicated disease like ALS will succeed in significantly impacting disease progression.
GWG Votes	**Is the project well planned and designed?**
Yes: 11 **No:** 0	• The goal now is to progress the candidate toward IND-enabling studies, building upon their successful experience conducting pre-IND meetings with the FDA for another ASO and out-licensing to a major pharmaceutical company. Thus, this is a team with excellent previous ASO expertise. • The goal of the project is a pre-IND submission. The application appropriately outlines the necessary activities, including product synthesis and assessment of purity, development of biomarkers (e.g. CSF levels of UNC13A in exosomes), pharmacokinetics and toxicity (including in a relevant preclinical model) dosed intrathecally as proposed in eventual clinical trial, and measures of clinical efficacy such as changes in ALSFRS-R, and S2VA PET scan. Note that the application includes prior correspondence with the FDA on a pre-IND submission for a different ASO targeting a different neurodegenerative disease target. This provides a good template for the eventual FDA interaction regarding the candidate. • In respect to these positive comments, there is a significant concern that the in vivo studies

	examining the duration of ASO-mediated UNC1A upregulation are minimal. Experiments to examine this concern are proposed, but this may be a pivotal concern for the success of this approach. • There are many unanswered questions in the broad scientific community about the durability of ASO expression and effects on protein levels that are required to provide therapeutic benefit. Moreover, the effects of ASO therapy on spinal muscular atrophy have been very exciting. Thus, there are reasons to be positive, but if it were the case that UNC13A levels in vivo were only elevated for a brief period, and that frequent intrathecal injections might be required, this is a topic of central concern. It seems entirely reasonable for CIRM to pay particular attention to this, even to make it a go/no-go criterion for continued funding. • Applicants should have presented some data on persistence of the ASO after treatment, as well as persistence of the resultant increased UNC13 protein.
GWG Votes	**Is the project feasible?**
Yes: 11 **No:** 0	• The project is clearly feasible, as indicated by the prior development and out-licensing of a separate relevant ASO . This is also an indication of the quality of the work of this team. • The team has lots of prior experience with ASO development; they clearly know what to do. • This is a well-constructed program with clear timelines and risk mitigation strategies. There is a strong team in place with the necessary expertise for many aspects of the proposed project. As needed, the proposal outlines partners for selected specialized activities including toxicity studies, and assessment of ASO purity. • While there are several potential bottlenecks, the milestones proposed are likely to be achieved within the indicated timeframe. • There are clearly several risks associated with the proposed project including off-target effects of the candidate, and hazards of intrathecal injection. The application appropriately outlines risk mitigation strategies.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 11 **No:** 0	• There is an excellent discussion of the DEI needs related to this project. • DEI principles are very well considered. • Part of the proposal promises to generate more diverse bank of iPSC for drug evaluation, which is very good. However, the application suggested potentially only 3 new lines, which is much too few to address DEI concerns. • Part 1 includes a robust discussion of the incidence and prevalence of ALS among ethnic communities, including those with high unmet needs. Part 2 is a well-developed plan to target those diagnosed with ALS and FTD. They have a clearly articulated plan to work with the patient advocacy community to ensure that enrollment meets their well defined underserved community objectives. Part 3 reflects the applicant's plans to incorporate a panel of patient iPSCs from diverse racial/ethnic groups in a proprietary platform to ensure that their result is applicable to all patient populations. • The application makes clear the prevalence of ALS among males>females, in various ethnic/racial groups and addresses strategies to ensure diverse representation by deriving iPSC lines from a diverse group of subjects. • The application outlines steps the team will take to interact closely with the ALS patient and the ALS advocacy community to ensure that their relevant perspectives and experience will be taken into account.

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: 10.0

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	1	• Part 1 includes a robust discussion of the incidence and prevalence of ALS among ethnic communities, including those with high unmet needs.

response		Part 2 is a well-developed plan to target those diagnosed with ALS and FTD. They have a clearly articulated plan to work with the patient advocacy community to ensure that enrollment meets their well defined underserved community objectives. Part 3 reflects the applicant's plans to incorporate a panel of patient iPSCs from diverse racial/ethnic groups in our proprietary platform to ensure that their result is applicable to all patient populations. • The development of this product definitely serves the unmet medical needs of CA's diverse ALS patient population. • The applicant seems well positioned to include diverse perspectives and experience.
6-8: Responsive	0	*none*
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-16192
Title (as written by the applicant)	Targeting pancreatic cancer with Allogeneic Off-the-Shelf PSCA-CAR NK cells
Translational Candidate (as written by the applicant)	PSCA-CAR_sIL15 NK cells derived from CD34(+) umbilical cord blood (UCB) hematopoietic stem cells (HSC)
Area of Impact (as written by the applicant)	Patients with metastatic pancreatic cancer or other cancers that highly express PSCA
Mechanism of Action (as written by the applicant)	PSCA-CAR_sIL15 NK cells are umbilical cord blood-derived CD34+ HSCs that are engineered to target PSCA and express soluble IL-15, and then are differentiated into NK cells. The cells can target PSCA positive tumor cells and the IL15 secreted by PSCA-CAR_sIL15 can activate T cells and NK cells in the tumor microenvironment.
Unmet Medical Need (as written by the applicant)	Pancreatic cancer (PC) is highly lethal, with a 5-year overall survival rate of 9%, and is the third leading cause of cancer-related death after lung and colon cancer. Pancreatic cancer disproportionately affects Black Americans. Successful translation of our safe, "off-the-shelf" cellular therapy of PSCA-CAR_sIL15 NK cells will diminish the life-threatening clinical manifestations of metastatic PC patients.
Project Objective (as written by the applicant)	Complete Pre-IND submission and finalize IND plans
Major Proposed Activities (as written by the applicant)	• Manufacture PSCA-CAR_sIL15 NK cells and PK/PD study • Pharmacology toxicity and optimize treatment schedule of PSCA-CAR_sIL15 NK cells in efficacy testing • Confirm efficacy of PSCA-CAR_sIL15 NK cells under optimized and safe conditions and Pre-IND submission
Statement of Benefit to California (as written by the applicant)	Pancreatic cancer (PC) is highly lethal, with a 5-year overall survival rate of 9%, and is the third leading cause of cancer-related death after lung and colon cancer. Pancreatic cancer disproportionately affects Black Americans. Successful translation of our safe, "off-the-shelf" cellular therapy of PSCA-CAR_sIL15 NK cells will diminish the life-threatening clinical manifestations of metastatic PC patients.
Funds Requested	$6,036,000
GWG Recommendation	**(85-100): Exceptional merit and warrants funding, if funds are available**
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 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	4
Highest	93
Lowest	80
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: 11 **No:** 1	• Metastatic pancreatic cancer is one of the deadliest cancers. This CAR-NK cell-based cell therapy may improve the prognosis for patients. • There exists a tremendous need for more effective treatments for pancreatic cancer. The proposed approach provides prospects for significant improvement in therapeutic outcomes for these patients. • There is a significant unmet medical need for new therapies for pancreatic cancer. • The product is a gene-based therapy that has good potential for providing a cell-based product that improves pancreatic cancer patient care. The product is made through genetic manipulation, specifically retroviral transduction of chimeric antigen receptor constructs to render NK cells specific for an antigen highly expressed on pancreatic cancer. • Because NK cell therapy has the potential to use off-the-shelf allogeneic cells, it can eliminate the manufacturing time for autologous CAR-T products, be produced in batches large enough to treat over 200 patients, and reduce overall costs of manufacturing and testing. Patients will benefit from the potential of chimeric antigen receptor targeted immune cells. Health care providers will have rapid access to an off-the shelf product. • A panelist noted a potential concern with off-tumor target killing. • A reviewer has serious concerns about the efficacy of the product on this disease, pancreatic cancer, since there is no design to counteract the solid tumor microenvironment.
GWG Votes	**Is the rationale sound?**
Yes: 11 **No:** 1	• The off-the-shelf strategy could have significant benefits. • The use of off-the-shelf cells is a big boost compared to CAR-T cells. • The scientific and clinical rationale are based on prior experience with NK-based product development, proof of concept studies that show good results with reduction of pancreatic tumor burden in mice, all using batches of a cryopreserved product that could potentially treat over 200 patients based on one manufacturing campaign. • The rationale for assessing chemotherapy in combination with the cellular product is based on prior information showing upregulation of the targeted tumor antigen following chemotherapy. • The experimental data included in the application supports the rationale. Supportive proof of concept studies include: in vitro killing of PSCA tumor cells by the CAR-NK product; enhanced in vivo survival of tumor burdened mice treated with the CAR-NK product; and lack of toxicity in mice treated with the CAR-NK cells. There was also in vivo evidence showing the improved efficacy of combination therapy with gemcitabine to improve CAR NK cell therapy. • The data from preliminary preclinical and CMC studies support further development of the product. The proposed mechanism of action due to CAR-NK tumor lysis, the upregulation of the CAR-NK target by chemotherapy, and the data showing reduced tumor burden in a mouse model all support development of the product. In addition, the proposed product addresses the significant problem of the suppressive tumor microenvironment by addition of a soluble cytokine which the applicant has shown to increase NK activation, survival and persistence. • CAR-NKs have shown limited efficacy in heme malignancies such as leukemia and lymphoma. However, their efficacy in solid tumors remains limited, let alone a recalcitrant tumor like that observed within the context of pancreatic cancer. The applicant does not show any clear data that CAR-NK cells are going to be effective in an actual solid tumor environment. • The rationale is not strong, since the microenvironment is not addressed.
GWG Votes	**Is the project well planned and designed?**
Yes: 12 **No:** 0	• All proposed activities are essential, and the timeline seems reasonable to accommodate CIRM's mission to deliver a transformative regenerative medicine genetic cell-based therapy for pancreatic cancer treatment. • All activities are well designed. • This is a strong team with a good track record and support from the host institution. • The project includes an abundance of proof of concept safety and efficacy studies,

	manufacturing and characterization plans. These activities will support successful completion and submission of a pre-IND submission package. FDA evaluation of the preclinical package will contain recommendations for IND-enabling preclinical studies. The applicant should be aware that the pre-IND submission will need to include a well-constructed clinical plan as well as CMC and preclinical information. • The program is consistent with quality by design principles, since it will provide initial data to achieve understanding of critical quality attributes, critical material attributes, process design and critical process parameters.
GWG Votes	**Is the project feasible?**
Yes: 12 **No:** 0	• The proposed timelines for product manufacture, PK/PD studies, pilot safety studies, optimization of proof of concept and confirmation efficacy studies, and pre-IND preparation and submission all seem well coordinated and reasonable. In a 17-day manufacturing process, the applicant can make enough CAR-NK cells to treat 240 patients from a single umbilical cord blood (UCB) unit. • The host institution has extensive CAR T cell clinical trial experience including experience with a CAR-T for prostate cancer. The proposed team also has complementary CAR-NK applications for FDA INDs. • The application team is part of an NIH sponsored Cancer Center of Excellence. The institution houses three GMP facilities dedicated to manufacturing stem cells, immune cells, and viruses. The program operates under an extensive set of SOPs covering all aspects of its activities, ensuring adherence to rigorous quality control standards in line with expert organizations and FDA regulations. The onsite GMP facility is licensed in California and has suitable manufacturing infrastructure, equipment, and staff with appropriate and extensive expertise. The PI has spearheaded successful execution of two engineering runs and five GMP runs for a separate CAR-NK study. • The applicant is exploring scale-up manufacturing in their laboratory. It is not clear that the 400 square foot laboratory as described in the application will be suitable for all aspects of manufacturing. These plans should be clarified. Also, it is likely they will receive appropriate feedback and support, since the applicant is part of an institution with two decades experience in CAR T cell GMP manufacturing. The team has successfully manufactured CAR NK cells. • The risk mitigation and financial contingency plan is appropriate to the institution and the applicant team. Identified risks include: potential delays due to umbilical cord blood availability; potential delays of the process transfer to GMP facility; and potential delays due to GLP-manufacturing failures. The contingency plans are reasonable and financial risk will be covered by the applicant organization as confirmed by a letter of support. • Regarding clinical risk, CAR-NK cells derived from stem-like umbilical cord blood NK cells have proven safe in the clinic without inducing graft-versus-host disease, CRS, neurotoxicity, or measurable inflammatory cytokines such as IL-6. The applicant will be prepared to follow standard treatment for management of these complications as needed including standard CRS therapy with steroids or anti-IL-6 receptor antibody treatment. In case of ≥ grade 4 toxicity without effective treatment options, the clinical team can use a clinical grade antibody that has been approved in the US for the treatment of solid tumors to remove the CAR-NK cells.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12 **No:** 0	• This product is not restricted by HLA matching and cells sourced from donors of any population group could be used to treat recipients from any population group. • Importantly, the product is designed as an "off-the-shelf" cell therapy that would be readily available and suitable for any patient, irrespective of their race, ethnicity, age, or socioeconomic background. The project serves the unmet need for improved pancreatic cancer therapy across the diverse California population. • The applicants uphold principles of DEI within their technical plan. • The sponsor projects a cost of approximately $2,000 per dose for this "off-the-shelf" product, which is a significant improvement for greater patient access across diverse socioeconomic populations. • The applicant is part of, and participates in, a center with multiple programs and achievements addressing cancer burden and care disparities. Some notable efforts include: implementation of community responsive cancer screening education, mobile screening units, participation with the CIRM Alpa Clinic Network to harmonize and develop best practices to address social determinants of health, prioritizing minority recruitment in clinical studies, and expanding the center's influence in local and state policy development. • The applicant institution and the sponsors also participate in a Community Advisory Board

	(CAB) where members represent key health sectors (community hospitals and clinics, focused health advocacy groups, cancer advocacy groups, equity focused community organizations, health professional organizations, and faith-based organizations that span the local community area). ● This was adequate for this stage of development. ● The application presents an adequate DEI plan. ● The DEI section is generic.

DIVERSITY, EQUITY, AND INCLUSION (DEI)

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

DEI Score: 6.0

Up to 7 patient advocate and nurse members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	0	*none*
6-8: Responsive	2	● This project presents a significant opportunity to advance DEI success for treatment of refractory pancreatic and perhaps other cancers with an off-the-shelf, inexpensive treatment that may be delivered in an outpatient rather than hospital setting. Very exciting. ● The DEI plan however was rather disappointing: the plan seems to rely most heavily on the applicant institution's distinguished record (top ten nation wide in hospital diversity rankings) rather than specific actions for this research effort. For example the DEI for this project will be overseen by the person who is in charge of all DEI activities for the institution. ● I thought the discussion of the ethnic variance of PC in outcomes and incidence was less helpful as compared to other applications reviewed. The discussion of the issues as they affect Black men as contrasted with Black women did not seem particularly useful. ● The strong point of this proposal is that this treatment is off-the-shelf and inexpensive. This could radically effect treatment access for all groups, particularly those with lesser socioeconomic means. However, the applicant seems to have delegated the issue of how to make sure that access is actually gained to an advisory board and a community alliance. ● It is certainly the applicant's goal to incorporate perspectives of those who will benefit using the multi-ethnic community advisory board, but once again the actions for this specific proposal are not spelled out.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-16070
Title (as written by the applicant)	Genetic Therapy Targeting mHTT mRNA to Treat Huntington's Disease
Translational Candidate (as written by the applicant)	An orally administered small molecule that induces the destruction of mutant huntingtin mRNA to treat Huntington's disease
Area of Impact (as written by the applicant)	Huntington's Disease
Mechanism of Action (as written by the applicant)	Our genetic therapy manipulates a protein coding mRNA in brain cells by precisely binding to an RNA complex that induces a modification of the mRNA, resulting in destruction of the mutant huntingtin mRNA that causes Huntington's disease. This therapy will be an oral drug that patients will take daily to prevent the progression of Huntington disease.
Unmet Medical Need (as written by the applicant)	Huntington's disease (HD) has a high unmet medical need. Current therapies fail to halt the progressive nature of HD. It is a devastating neurodegenerative disorder characterized by motor dysfunction, cognitive decline, and psychiatric symptoms. Some medications can alleviate symptoms, but treatments that modify the course of the disease are lacking. Existing therapies primarily focus on managing symptoms rather than addressing the underlying cause.
Project Objective (as written by the applicant)	Pre-IND Meeting and readiness
Major Proposed Activities (as written by the applicant)	• Demonstrate that candidate is potent in the target neuronal cell type that is affected in Huntington's disease • Complete the toxicology profile for the candidate in animals to demonstrate it's safety for clinical trials • Prepare data package to initiate IND enabling studies and discussion with FDA to initiate clinical trials for Huntington's disease
Statement of Benefit to California (as written by the applicant)	The California applicant organization aims to advance a candidate for Huntington's disease (HD), potentially providing a groundbreaking treatment. The success of this research could enhance patient well-being, bolster the biotech sector, and position California as a leader in neurodegenerative disease innovation, fostering economic growth and scientific advancement within the state.
Funds Requested	$3,994,237
GWG Recommendation	**(85-100): Exceptional merit and warrants funding, if funds are available**
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 87

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

Mean	86
Median	87
Standard Deviation	3
Highest	90
Lowest	80
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: 12 **No:** 0	• Overall, this grant has the potential to make a significant impact. There remains significant unmet medical need for Huntington's disease. • Huntington's disease is a devastating neurodegenerative disorder for which there are no effective treatments or cures so the product meets an important medical need. • In addition to the potential therapeutic impact, the candidate has the benefits of non-invasive dosing. • This gene therapy to target mHTT to treat Huntington's disease would have a high potential for impact given there are no approved treatments or cures. • The proposal is significant because it provides a small-molecule based approach to modification of gene expression in the setting of Huntington's disease, which currently has limited treatment options and represents an unmet medical need. • The project provides a novel small-molecule based modality to alter the outcome of RNA expression. Successful translation would significantly improve patient care due to ease of administration, lower cost, and availability from pharmacies rather than specialized medical centers. • Successful translation would provide great practical and impactful beneficial results for patients care due to ease of administration, lower cost, availability from pharmacies rather than specialized medical centers. Health care providers would have a treatment option that would be in pill form rather than more technical and complicated modes of administration.
GWG Votes	**Is the rationale sound?**
Yes: 12 **No:** 0	• The reduction of mutant HTT to reduce neuronal death is a good strategy based on scientific rationale. • The rationale is supported by other similar efforts and by the applicant's preliminary data. • The therapy has a sound scientific rationale. The candidate binds to an siRNA complex that has been shown to effectively reduce the mutant Huntingtin protein. • The overall rationale is sound. The preliminary data suggest that the drug compound can knock down mutant huntingtin protein. • There is convincing evidence that induction of cryptic alternate splicing can induce nonsense mediated RNA decay and reduction of the harmful version of Huntingtin protein. • The scientific rationale is sound. The applicant has convincing in vivo evidence in a human mouse xenograft model that the drug candidate changes splicing of mHTT RNA such that the harmful RNA enters a well studied nonsense mediated decay (NMD) pathway of RNA degradation, leading to reduction of expression of the mHTT protein. • Reduction of the mutant Huntingtin protein could lead to preservation of neuronal cell function and numbers in patients. There could possibly be reversal of severity. • The proof of concept and preliminary preclinical data provide excellent support for further development of the product.
GWG Votes	**Is the project well planned and designed?**
Yes: 11 **No:** 1	• This well designed project seeks to generate a comprehensive efficacy and safety package and clinical development plans and to enter human clinical trials in the next 2 years. • The application is well-written with multiple milestones and an engaging nonclinical testing strategy and robust CMC development program to support development. • All proposed activities are essential, and the timeline seems reasonable to accommodate CIRM's mission to deliver a transformative regenerative medicine genetic small-molecule based treatment for Huntington's disease. • The program is consistent with Quality by Design principles. It will provide initial data to achieve understanding of critical quality attributes, critical material attributes, process design and critical process parameters. • This is a well-constructed program that is consistent with quality by design principles. • The proposed preclinical studies are well designed, include multiple species, include appropriate in vitro human cellular studies, and appropriate animal safety, PK/PD studies, and efficacy animal studies. The applicant has engaged appropriate internal and external expertise to draft a protocol synopsis for regulatory purposes detailing key parameters

	including study objectives, design structure, patient population, endpoints, dosing, safety assessments, and statistical analysis approaches for the phase 1 trial. • Proposed activities are essential, and the timeline is ambitious, but feasible. • Due to the lack of specificity for mHTT RNA, the FDA likely will ask for a broader preclinical assessment of toxicity and safety as part of the final GLP studies. The proposal focuses on neural and CNS tissues and includes heart, liver, and muscle assessments. It may be wise to broaden the spectrum of non-neural tissues early during the grant-supported studies in case of unexpected toxicities in other organs (e.g., pancreas, thymus, lymph nodes, spleen, etc). Such an approach could be considered as an addition to the planned rodent toxicity screen. • An attractive proposal is to conduct a study to support a machine learning/AI approach to interspecies splicing risk assessment that will support selection of informative animal species for toxicology studies. • There remains a major risk related to the candidate's efficacy. It is unclear if this will work in a relevant pre-clinical model, either an organoid system or a mouse model of HD (such as the BACHD mouse model). The applicant should generate some initial pre-clinical data in a clinically relevant model demonstrating that their candidate can actually mediate phenotypic correction of HD.
GWG Votes	**Is the project feasible?**
Yes: 12 **No:** 0	• Yes, the proposal is feasible and the milestones are achievable. • The applicant team has a viable contingency plan to manage risks and delay. • Members of the applicant team combine skills in program management, chemistry, biology, translational genomics, drug metabolism and pharmacokinetics, clinical pharmacology, and medical leadership. • The project appears to have feasible milestones for chemistry, manufacturing, and controls (CMC), clinical, and planned pharmacology/toxicology studies. • The project is ambitious but feasible. • The team is well qualified but relies heavily on CROs and external consultants. • This project is feasible with the team that is either in house or contributing via contracts. • The contingency plans are likely viable. • A panelist notes an absence of phenotype rescue data, and they are not clear regarding mitigation plans should phenotypic correction not occur. • There were some concerns that a discordance between reduced protein and effective transcription resulting in no phenotypic correction of Huntington's symptoms under the limited testing to date. This could be further explored with dose-ranging studies. • It appears almost all of the requisite resources and personnel are available for the project. One area that may need clarification is the needed expertise to use transcriptomic data to build proposed AI-based predictive toxicity screens across species.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12 **No:** 0	• Yes, this project has the potential for development of a widely applicable product that would cross diversity barriers, since the drug would have no expected major differences in mechanism of action across populations. • Yes, the sponsor has carefully considered epidemiological data across these categories in terms of differential disease prevalence, and disease severity. Although the sponsor found no significant evidence to suggest impact of gender, race, ethnicity or age alone on modifying course of disease or survival, they are committed to study this further with appropriate in vitro experiments from diverse biospecimens. • Yes, the applicant leaders engage the HD community (as noted in the Letters of Support), and will discuss clinical trial design to make sure they include concerns of all patients and caretakers affected by Huntington's disease. • DEI was appropriately addressed. • The oral administration would mean a cheaper and more accessible treatment. • Yes, overall the applicant does a good job here. • The applicant presents an adequate DEI plan.

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	2	• The application presents an adequate DEI plan. • Differences between genders have been noted, and testing designed with those differences in mind is presented. • Geographic differences may exist. This is very interesting, and the testing already planned can accommodate and measure those differences.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-16236
Title (as written by the applicant)	A targeted antisense oligonucleotide therapeutic for Timothy syndrome
Translational Candidate (as written by the applicant)	Timothy syndrome 1 (TS1) is a rare, potentially fatal disorder affecting the brain and heart, and is caused by genetic mutations in a calcium channel.
Area of Impact (as written by the applicant)	Neuropsychiatric symptoms in TS1 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	$5,944,166
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	84
Median	86
Standard Deviation	5
Highest	88
Lowest	70
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	9
(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: 11 **No:** 1	• This is a resubmission of a proposal that seeks to develop a targeted antisense oligonucleotide therapeutic approach for Timothy syndrome 1 (TS1) - a rare genetic life threatening disorder affecting calcium signaling in the nervous system and heart - the syndrome is severe. The response to previous concerns is overall excellent. • TS1 patient longevity has increased due to medical intervention for heart problems (from 2 to 20 years) but neurological symptoms worsen and highly impact quality of life. • TS1 is usually diagnosed early, allowing for early intervention. ASO approaches have proven valid throughout the central nervous system. • Spinraza, a ASO already in the clinic, contains the same backbone and chemical modification as the proposed TS1 candidate. In addition, a single injection of ASO into large animals showed that ASO can be effectively delivered. • The proposed ASO drug product has the potential to impact patients suffering from Timothy Syndrome. • The proposed product for TS1 addresses an unmet medical need due to the rarity (less than 100 patients globally), but it will not accelerate the development of stem cell or other new technology. While focusing on rare diseases aligns with CIRM's mission, the small patient population presents challenges for commercialization, requiring creative approaches to succeed. This remains unaddressed in the application. • Since ASOs are approved, their use in this context does not significantly advance the field, as their application for targeting specific genetic variants is already established. The grant's reliance on ASOs for targeting specific genetic variants limits its applicability to other pathogenic variants within the same gene. • Concern over impact.
GWG Votes	**Is the rationale sound?**
Yes: 11 **No:** 1	• Yes, the rationale for using an ASO drug product is rooted in data that indicate the potential to rescue TS1 variant expression. • The product is a novel ASO therapy that targets a TS1 variant by altering exon splicing specifically in the brain. • The applicant proposes ASO injection. If efficacious, therapy could address frequent, devastating neurodevelopmental and psychiatric symptoms associated with TS1. • This proposal addresses the lack of an animal model for TS1 by using human-derived neurons and organoids to demonstrate the efficacy of the candidate ASO in rescuing the TS1 phenotype. The study's focus on exon expression, ion flux kinetics, calcium dynamics, and interneuron movement defects provides some support for the ASO's potential therapeutic effects. However, a more explicit discussion of how these findings will translate to potential clinical outcomes for TS1 patients would be useful.
GWG Votes	**Is the project well planned and designed?**
Yes: 11 **No:** 1	• From a CMC perspective, the project is well planned. Additional time is available in case CMC risk mitigation activities are required. • Previous critiques were that there is no animal or other model to test efficacy. In response to that, the applicant developed a TS1 organoid model that recapitulates neuronal defects, which can be rescued by ASO. • The applicant also shows that ASO can rescue electrophysiologic and interneuron migration phenotypes in TS1-derived neural assembloids that have been transplanted into mice. The manuscript is under review in a high impact journal. • ASO showed minimal toxicity and minimal off-target effects. • There is concern over the lack of contingency plan.
GWG Votes	**Is the project feasible?**
Yes: 12 **No:** 0	• The lab will test the TS1 ASO on neural organoids and forebrain assembloids generated from TS1 human stem cell lines over a wider range of concentrations and using the purified RNA drug. • Applicant will conduct pilot pharmacology and optimal dosing. • Safety studies in rodents and large animal studies will be performed by a contract research organization using standard measures. Animals will be observed for side effects. • Based on the activities and timelines provided, the project is feasible from a CMC perspective. • Highly experienced, but too many people with salary are listed considering that over 50% of

	experiments are conducted by third parties. ● Minimal contingency plan.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12 **No:** 0	● Previous concerns of finding enough patients have been addressed.

DIVERSITY, EQUITY, AND INCLUSION (DEI)

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

DEI Score: 7.0

Up to 7 patient advocate and nurse members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	0	*none*
6-8: Responsive	1	● Adequate DEI plan. ● This is a resubmission that previously received a score of 7, and has no fatal flaws. I concur with the comments on the original submission.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN4-16091
Title (as written by the applicant)	Purification of Human Hematopoietic Stem Cells (HSC) for Clinical Stem Cell Transplantation
Translational Candidate (as written by the applicant)	Two new monoclonal antibodies anti-CD34 and anti-CD90 and protocols to purify cancer-free and/or T cell free human hematopoietic stem cells (HSC) for clinical transplantation.
Area of Impact (as written by the applicant)	The development of hematopoietic stem cell (HSC)-based therapies, starting with rescue of metastatic breast cancer (MBC) patients with their own cancer-free HSC.
Mechanism of Action (as written by the applicant)	The mechanism is using highly purified HSC to regenerate the blood and immune systems without contaminant disease-causing cells. For cancer patients who undergo transplantation with their own stem cells, harvesting stem cells from blood may also collect circulating cancer cells. We propose to add a step of purification to current HSC enrichment protocols. We'll develop specific reagents and cell sorting protocols to yield cancer-free human HSCs for a safer clinical transplantation.
Unmet Medical Need (as written by the applicant)	Current transplantations of blood-forming cells are hindered by the presence of contaminating cells; mobilized blood and CD34 selected cells from women with MBC have cancer cells in the grafts. Pure CD34+90+ HSC rescue patients from high-dose chemotherapy (HDCT), lack cancer cells, prolong survival in about 66% of patients, and cure 33% otherwise incurable. Purified HSC lack donor T cells and can induce transplantation tolerance to HSC donor organs or tissue stem cell transplant without graft vs host disease.
Project Objective (as written by the applicant)	Producing reagents and protocols for HSC isolation
Major Proposed Activities (as written by the applicant)	• Antibody production and validation to generate the reagents for clinical isolation of human HSC. • 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 purified HSC, cell viability, purity, and biological function.
Statement of Benefit to California (as written by the applicant)	We propose to generate and provide reagents for HSC purification in non-profit settings for academic transplantation units, and free for underserved patient populations. Our aim is to be the driver to expand the use of pure HSC isolation and transplantation for a variety of human diseases, beginning with metastatic breast cancer. 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	$1,499,683
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	86
Median	85
Standard Deviation	3
Highest	90
Lowest	80
Count	12
(85-100): Exceptional merit and warrants funding, if funds are available	7

(1-84): Not recommended for funding	5

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/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 **No:** 0	• The development of these monoclonal antibody (mAb) reagents and their validation in clinical-grade purification of HSC has the potential to address/overcome a bottleneck in transplantation medicine. • The overall project - developing a tool for enabling highly purified CD34+CD90+ cells - is important for the development of stem cell therapies and gene modified stem cell therapies. The technology will meaningfully contribute to the overall field. • The technology may be an improved way to derive HSC for a variety of other therapeutic approaches that currently rely on isolating CD34+ cells. • These diseases impose a burden upon patients and providers, and significant morbidity and mortality is associated with alternative therapies. • The platform is strong, and the potential is broad. Clinical adoption for use in breast cancer may be less swift than the investigators propose. • There was a lot of discussion regarding whether the technology would make a difference for breast cancer patients. There may be better cancer types for the first clinical evaluation. • It is unclear that this product will make an impact in the treatment and standard of care of metastatic breast cancer and other solid tumors. • The technology lacks significant potential for impact in auto-transplant for solid tumors. Fund this as a technology, not for the specific indication.
GWG Votes	**Is the rationale sound?**
Yes: 11 **No:** 0	• Yes, the overall rationale for developing a novel method for automated cell sorting of highly pure CD34+CD90+ HSC is sound. This will be important for developing gene-edited autologous HSC therapies. Going forward, it is recommended that the applicant partner with a gene-editing company or investigator to develop this technology within the context of gene-edited stem cell therapies. • Regarding the potential for removing circulating tumor cells: the applicant used PCR to detect a surrogate for circulating tumor cells (spiked cells from a breast cancer cell line). Preliminary data with a highly sensitive assay demonstrated that either no or minimal cancer cells remained after purification with the proposed technology. • Purifications antibodies tested in an earlier clinical trial induced phagocytosis, so the applicant engineered new mAbs with disrupted Fc effector functions. Preliminary data show significant reduction of phagocytosis. The applicant will express these mAbs in CHO cells to make new mAbs for the proposed work. • The platform can be extended broadly to genetic hematologic diseases and patients with other cancer metastases. • Current proof-of-concept data show high purity HSC using a two-step process. • The rationale for using this tool to develop an HSC cell therapy for breast cancer and solid tumors is significantly weaker.
GWG Votes	**Is the project well planned and designed?**
Yes: 11 **No:** 0	• This is a resubmission. The applicant provides a detailed, improved plan and design with clear metrics, outcomes, risk mitigation plans, and alternative strategies. • Overall, this is a well-designed and well-planned project. • The applicant will evaluate the new mAbs and new protocols using closed system cell sorters currently used for other GMP cell processing. Current proof of concept data show high purity using a two-step process. The team are working with a vendor to adopt the process to a single-step purification. • Studies to date have all been done with cells from healthy donors. The investigators have provided an explanation for why they cannot ethically obtain mobilized PBSC from MBC patients.
GWG Votes	**Is the project feasible?**
Yes:	• This is a highly qualified team. As noted in the proposal, the PI has been at the forefront of

11 **No:** 0	HSC biology for decades and has assembled a team of experts to support the implementation of the proposed project. • The host institution has a GMP cell manufacturing facility with all the requisite equipment. The team has developed arrangements with key vendors to allow for evaluation of their protocol using cell sorters currently used clinically, to enable their protocols to easily fit into clinical cell sorting centers. • The team and resources are clearly equipped to carry out the project, and milestones are well described. • This is a feasible project.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 11 **No:** 0	• This applicant does a good job of upholding principles of DEI. • Primarily, their plan is to address this issue by providing broad access to the product. They plan to manufacture and provide the mAbs at cost or for free, as well as the protocols, for any medical institution interested using the technology for clinical trials. • The applicant discusses disparities in MBC, and show reliance on the host institution's DEI efforts.

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	1	• The applicant institution has a strong track record and DEI focus. Key factors have been taken into consideration related to product development and DEI enhancement. • The proposal describes the planned first proposed use of the technology in MBC, and demographic data for this indication have been assembled. The applicant notes significant racial disparity in MBC incidence, prognosis, and mortality with poorer outcomes for Black women. • The limited clinical trial data to date suggest that the proposed purification process would not discriminate based on race for any individual seeking to part in a downstream clinical trial. • To assure that the methodology is compatible with different ethnicities in California, the team will include samples from donors of different racial and ethnic groups representative of California's diverse population in their process development. • The host institution is well-known for their strong DEI efforts with respect to patients, has a strong track record, and a broad catchment area that can draw in a diverse patient population. • The host institution's cancer institute recognizes that disease pattern, clinical presentation and therapeutic response can vary dramatically based on several factors including race/ethnicity, ancestral background, socioeconomic status, and gender. • The liaison with predominantly Black community health providers allows the PI and faculty to visit the clinics to explain the science behind the MBC program. • A clinical site in a lower-income, racially diverse city outside CA is being considered to draw upon increased access to a Black population.

		• Patient group interactions will be part of the applicant's future efforts as disease areas continue to come into focus.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-16030
Title (as written by the applicant)	Evaluation of an ex vivo lentiviral gene therapy for the treatment of Angelman syndrome (AS)
Translational Candidate (as written by the applicant)	Lentiviral (LV) transduced CD34+ cells
Area of Impact (as written by the applicant)	Area of impact is Angelman syndrome (AS). Lentiviral vector manufacturing and CD34+ cell drug product manufacturing are identified bottlenecks.
Mechanism of Action (as written by the applicant)	Lentiviral (LV)-modified autologous blood stem cells will be used to transplant patients with their own cells. Some of the resulting blood cells will migrate to the brain and secrete the enzyme Ube3a (which is missing in Angelman syndrome (AS) patients) to cross correct the surrounding neurons.
Unmet Medical Need (as written by the applicant)	Currently there is no cure for Angelman syndrome (AS)
Project Objective (as written by the applicant)	Pre-IND
Major Proposed Activities (as written by the applicant)	• Manufacturing - Plasmid, lentiviral vector, CD34+ cells • Safety assessment - both the lentiviral vector and cells transduced with the lentiviral vector • Regulatory - submit a complete pre-IND package
Statement of Benefit to California (as written by the applicant)	Angelman syndrome (AS) is a rare genetic disorder with relatively equal distribution among males and females and ethnicities. An ex vivo hematopoietic stem cell gene therapy approach using lentivirus has proven to be an efficient means to replace a deficient enzyme in other CNS disorders via cross correction. The new therapy proposed here will provide a viable treatment for children born with AS in California and beyond the state borders.
Funds Requested	$6,289,988
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	85
Median	85
Standard Deviation	4
Highest	90
Lowest	75
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	10
(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: 12 **No:** 0	• The project is focused on developing a clinically meaningful treatment for patients with Angelman Syndrome (AS), a severe disease with no cure. • The proposal is to develop a lentiviral (LV) gene therapy approach for the treatment of AS, specifically, using CD34+ hematopoietic stem/progenitor cells (HSPCs) transduced with a LV expressing a secreted form of ubiquitin-protein ligase E6-AP (UBE3A). • AS patients have a normal lifespan, but severe mental/developmental defects. Addressing the neurological decline would increase quality of life. • Even if this approach is not curative it could considerably slow AS progression. • AS is a serious disease which manifests early in childhood and results in severe developmental delay, profound lack of speech, debilitating seizures, motor deficits, ataxia, dyspraxia/apraxia, sleep difficulties, anxiety, and aberrant behaviors. • Preclinical data and results from studies using the prior vector construct are highly supportive of potential impact.
GWG Votes	**Is the rationale sound?**
Yes: 12 **No:** 0	• Antisense oligo (ASO) therapy for AS has had promising results in patients, but the ASO approach does not address the full expanse of mutations that cause AS. Prior studies using LV to replace the UBE3A gene resulted in malignancies, likely due to LV integration into proto-oncogenes. • The applicant will use ex vivo gene therapy of autologous HSPC to be transplanted after myeloablative conditioning. The rationale is to provide a functional UBE3A gene that offsets the loss of UBE3A expression in the CNS. • The gene therapy component is an LV carrying the ubiquitin-protein ligase E6-AP (UBE3A) sequence under the control of a physiologic promoter. This could restore gene function. • HSPCs are a renewable source of macrophages. Some macrophages cross the blood brain barrier and become microglial cells. In this proposal the HSPCs are transduced with an LV that expresses a secretable version of UBE3A, an enzyme that is missing in patients with AS. The secreted enzyme is capable of cross correcting neurons in the surrounding brain tissue, ideally ameliorating the disease phenotype. • Prior clinical trials have used antisense oligonucleotide (ASO)-directed degradation of the AS form of UBE3A, indirectly reactivating expression of the paternal UBE3A allele in the CNS as a therapy for AS. This approach has its limitations. • The proposal is based on previous studies from other groups, such as from Adhikari, et al. that showed CD34+ cell rescue in a novel immunodeficient UBE3A-/+ mouse model. The applicant seeks to change the promoter used in the Adhikari, et al. study, since FDA has concerns about that promoter. • Targeting correction of a single gene deficiency with improved-promoter LV is a very sound principle. Preliminary data strongly support the approach.
GWG Votes	**Is the project well planned and designed?**
Yes: 10 **No:** 2	• Overall, the project is appropriately planned and designed to achieve meaningful outcomes. I had some issues figuring out if the data provided in the proposal came from the previous study from another group or the applicant, or as a collaborative effort. The team may be able to detail this more clearly. • Will expression of UBE3A be sufficient to improve neuronal defects, and result in significant improvement for AS patients? Will the therapy be affordable? • The project is very well planned. The team has considerable experience with similar approaches. • The proposal includes a contingency plan where a partner covers costs. • A prior FDA meeting identified appropriate assays.
GWG Votes	**Is the project feasible?**
Yes: 12 **No:** 0	• The proposed milestones and the expected project outcome are likely to be achieved. The PI has many years of experience with lentiviral technologies and has been involved in the development and manufacture of lentivirus for clinical use. • All aims are feasible, and the team is highly experienced. • Absolutely; the team has completed similar projects.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12 **No:** 0	• The applicant has a close collaboration with a patient advocacy organization that will address diversity. • AS is a rare disease. The world prevalence has been estimated based on its predominantly random occurrence, and relatively equal distribution among males and females and

	ethnicities. The proposal mentions plans to conduct studies involving a diverse cohort of patients. ● The applicant has addressed major DEI concerns.

DIVERSITY, EQUITY, AND INCLUSION (DEI)

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

DEI Score: 9.0

Up to 7 patient advocate and nurse members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	2	● The applicant's research indicates that natural history studies of AS lack population diversity, with underrepresentation of underserved communities. ● The applicant has a partnership with a foundation dedicated to people affected by Angelman Syndrome (AS). Among other efforts, the foundation has a global AS registry and a "Search and Rescue" campaign to lessen the burden of connecting with the advocacy group. The foundation has also piloted wearable technologies and at-home video assessments to assess treatment outcomes and reduce the need for patients to travel to a study site. ● The applicant has preliminary plans to address barriers to trial participation, with potential solutions including engagement of patients in the clinical trial design. Travel for the clinical trial will be reimbursed and translation services will be provided. ● A draft trial protocol will be developed to support a Pre-IND meeting and future IND filing, outlining outcome measures and practices to enable decentralization and inclusion of a diverse group of patients. This preclinical and future clinical work will be conducted at the applicant institution, which has a strong "inclusive excellence framework" for advancing DEI. ● Excellent DEI plan.
6-8: Responsive	1	*none*
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-16065
Title (as written by the applicant)	A Novel Gene Therapy to Target Glioblastoma via Custom-Engineered Adenovirus-Associated Viral Vectors
Translational Candidate (as written by the applicant)	Highly GBM-selective AAV-derived vector armed with a gene construct to target the key master regulator combination MePN in GBM.
Area of Impact (as written by the applicant)	The novel gene therapy, targeting common GBM molecular features, promises a broadly effective approach for GBM patients who have few treatment options.
Mechanism of Action (as written by the applicant)	The novel gene therapy involves the introduction of a targeting gene cassette that will be delivered directly into GBM cancer stem cells (GSC) using a highly potent rAAV vector derived from the clinically proven vector AAV2. The candidate is designed to deplete a combination of 3 master regulators MePN that are common in GSCs from different GBM tumors. Acute depletion of MePN in GSCs causes disruption in major pathways controlling the identity and survival of GSCs, leading to their death.
Unmet Medical Need (as written by the applicant)	Development of new therapies for GBM, the deadliest brain cancer in adults with few treatment options, is hampered by its heterogeneity. The proposed product addresses this unmet medical need by targeting the common GBM state that transcends the heterogeneity to create a broadly effective therapy.
Project Objective (as written by the applicant)	Pre-IND meeting to help guide trial strategies.
Major Proposed Activities (as written by the applicant)	• Develop a GMP-compatible process to produce our lead candidate for a planned pilot study. • Optimize a brain infusion method to deliver T6 and conduct biological activity studies to prepare for a pre-IND meeting. • Conduct a pilot safety study to determine a safe effective dose of T6 to confirm its in vivo efficacy to prepare for a pre-IND meeting.
Statement of Benefit to California (as written by the applicant)	In California like elsewhere, prognosis for GBM across racial and ethnic groups remains dismal. Development of new therapies is hampered by the heterogeneity of GBM tumors. Yet, GBM shows extensive clinicopathologic overlaps suggesting the presence of a common state. By targeting the common GBM state, it is possible to circumvent the heterogeneity. This approach promises a heterogeneity-agnostic, broadly effective gene therapy, bringing renewed hope to GBM patients in California and beyond.
Funds Requested	$5,927,453
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	85
Median	85
Standard Deviation	2
Highest	89
Lowest	80
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	9
(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: 12 **No:** 0	• The proposed drug product has the potential to impact the standard of care, and thus the lifespan, of patients with Glioblastoma (GBM). • Individuals with GBM have a median survival time of less than 15 months and five-year survival rate of only 5-7%. Surgical resection followed by radiotherapy with concurrent and adjuvant temozolomide remains the standard treatment for newly diagnosed GBM, but almost all patients experience recurrence within a year. Following recurrence, there are no viable treatment options. • Development of new therapies, especially for recurrent, refractory GBM is complicated by intra- and inter-patient heterogeneity, characterized by distinct subclones of glioma stem-like cells (GSC) with redundant growth signals and differential responses to therapy. • Overcoming the heterogeneity in GBM has been an intractable therapeutic challenge. The product is focused on eliminating glioblastoma stem cells using a gene therapy approach. • Glioblastoma continues to be a cancer in which survival rates are poor and treatment options are very limited. This proposal has the potential to have a meaningful impact on patient care. • The pathway analysis is extensive and thorough. If the hypothesis proves correct, this treatment could hit at the key points in tumor development and progression.
GWG Votes	**Is the rationale sound?**
Yes: 12 **No:** 0	• The clinical rationale is solid, and the work in patient derived tumors suggest broad application. • The fundamental research on tumor pathways is extensive and impressive. The group appears to have identified key points within the tumor survival and progression. • By focusing on master regulators (MR) that appear to govern shared GBM characteristics, there is the possibility of circumventing GBM heterogeneity. This group identified a core set of nine high-ranking MRs, organized into two hubs, which control three key pathways in GSC subclones across GBM tumors. Seven of these MRs are developmental factors, suggesting the GBM state may be driven largely by a developmental subnetwork. This may mean that targeting these pathways offers a safe therapeutic target, but thorough safety analyses will be critical (as noted under design). • The goal is to pioneer a first-of-its-kind, heterogeneity-agnostic gene therapy that targets GBM. The applicant has engineered highly efficient vectors derived from adeno-associated virus (AAV) to deliver a shRNA cassette designed to deplete the GBM state MRs in GSCs. • The lead variant shRNA candidate displays up to 40-fold higher efficiency at transducing GBM cells compared to wild-type AAV and other variants tested, and it achieves cure rates of 70-90% in patient derived tumor xenografts (PDX). • The applicants demonstrated successful convection enhanced delivery (CED) of AAV into a growing GBM tumor with 10-fold higher efficiency compared to a single intratumoral injection of the same viral dose. • Even with the suboptimal single intratumoral injection, the lead candidate efficiently covered the entire tumor, spread to the invasive front and peri-tumor region, and infected infiltrating GSCs and induced apoptosis. • The non-clinical pharmacology is impressive, and the team has clearly demonstrated an impact on tumor growth. There is a concern the fundamental mechanism of action has not been fully demonstrated. The product expresses shRNA constructs, but the application did not have data demonstrating an RNAi mechanism of action. Tumor growth is impacted and the pathways are impacted, but data showing the point of contact between the shRNA and target remain to be provided. • The rationale is sound from a CMC perspective. The additional details provided in the revised submission were thorough. • Proof of concept data are not sufficient.
GWG Votes	**Is the project well planned and designed?**
Yes: 12	• From a CMC perspective, the project is well planned, notably the use of reputable vendors to provide the necessary drug product materials. • Manufacturing, efficacy and clinical plans seem appropriate.

No: 0	• In the preclinical phase of pharmacodynamics and pharmacokinetics, they will use both sex- and age-specific PDX models in NSG mice to recapitulate the diversity of GBM patients. They will also use PDX from donors of diverse epigenetic subgroups, from both male and female patients, and whenever detailed demographic information is available, donors from different racial and ethnic backgrounds. • For pilot safety studies, they will use mice from four independent inbred and three mixed genetic backgrounds to measure local and systemic on and off target adverse effects of the lead candidate. In order to recapitulate as much as logistically possible, they will study genetically and racially GBM diverse patient populations. • It should be noted that safety studies lack analysis of normal stem and precursor cell populations that may still express the MRs. It would be appropriate and necessary to look at effects of the candidate and other vectors on cells of the sub ventricular zone and hippocampus, along with oligodendrocyte progenitor cells (OPC) that are widely dispersed in the adult brain. OPC are thought to be the major dividing cell in the adult brain, at least in rodents. • As noted the non-clinical safety plan is not well described, and what is outlined does not seem to be adequate.
GWG Votes	**Is the project feasible?**
Yes: 11 **No:** 1	• Yes, the project is feasible for manufacturing activities. The timelines appear appropriate. • The manufacturing processes involve the GMP-compatible plan of graduating culture vessel size from the standard small shaker flask format to small (2L) stirred tank bioreactors (BR) to large (10L) BRs using cells specifically optimized for suspension culture and large-scale efficient protein production. This is an an industry standard approach to produce rAAV for clinical applications. • A member of the applicant team was a founding director of a Vector Core Laboratory. They have developed multiple AAV vectors, plasmid DNA helpers, novel production platforms, and purification protocols that have now become industry standards. • Methods and assays pioneered by a team member's Vector Core lab were subsequently incorporated into large-scale GLP/GMP production protocols in the highly successful GMP facility. The center has developed and conducted AAV-based clinical trials with complex AAV products in neurodegenerative and muscular dystrophy diseases in humans and large animals. • For the manufacturing and efficacy studies, the milestones are appropriate and reflect comprehension of reasonable time frames. Adequate consideration has been given to potential failure points, the mitigations to address them and to compensate for most manufacturing changes (short absolute failure in efficacy or tolerability). • The non-clinical safety plan is high level at best and cannot be evaluated as it is described.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12 **No:** 0	• The project plan is appropriate in this regard. • The host institution actively promotes DEI among its students and physicians. The school prioritizes community health, patient access, and engagement, with a particular focus on historically underrepresented and underserved populations. • The community outreach and engagement office at applicant institution's Comprehensive Cancer Center (CCC) and Clinical Translational Science Institute (CTSI) also contribute to DEI efforts by informing diverse communities about cutting-edge treatments, including gene and stem cell therapies. • The latter offices also work with community advisory boards and the institution's strategic plan to bridge the gap between scientists and communities.

DIVERSITY, EQUITY, AND INCLUSION (DEI)

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

DEI Score: 7.0

Up to 7 patient advocate and nurse members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	1	• The purpose of this project is to develop a heterogeneity-agnostic gene therapy for glioblastoma. This cancer is the most common and lethal form of brain cancer, with a lack of curative therapies. • In terms of epidemiology, ~60% of patients are men. Compared to Blacks and Asian/Pacific Islanders, the incidence and mortality rates are higher in Non-Hispanic Whites and Hispanic patients. Lower SES is associated with increased mortality, which suggests disparities in access to care. • Identification of the therapeutic target is based on a dataset that includes independent expression profiles from both male and female patients with glioblastoma from different racial and ethnic groups and from the entire glioblastoma RNA-seq collection of 176 patients in the Cancer Genome Atlas. The latter includes patients from various geographic regions, as well as diversity in terms of gender, racial, ethnic and socioeconomic backgrounds. • In the preclinical studies, plans are in place to use sex-specific and age-specific models. Investigators are engaged with various advocacy groups and support groups that will assist with recruitment into the future clinical trials. • A key part of the investigator's DEI strategy is to engage with an Alpha clinic team to enhance the recruitment of a diverse sample of patients into the future clinical trial.
6-8: Responsive	1	• The application presents an adequate DEI plan
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-16022
Title (as written by the applicant)	Development of an AAV Epigenetic Gene Therapy for Gain-of-Function SCN9A Disorders and Chronic Pain
Translational Candidate (as written by the applicant)	An epigenetic gene therapy that represses Nav1.7 for long-lasting chronic pain relief
Area of Impact (as written by the applicant)	Gain-of-function mutation of Nav1.7 (primary inherited erythromelalgia (IEM) and small-fiber neuropathy) and chronic pain
Mechanism of Action (as written by the applicant)	The proposed candidate is an epigenetic gene therapy that represses Nav1.7, a sodium channel responsible for pain signal transmission, to treat chronic pain.
Unmet Medical Need (as written by the applicant)	There are currently no FDA approved drugs for inherited erythromelalgia (IEM), which is caused by a gain-of-function mutation in a sodium channel, Nav1.7. We propose epigenetic repression of Nav1.7 to provide a cure for IEM.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Process Development and GMP viral production • Safety Studies in Larger Animals • Potency Assay Development
Statement of Benefit to California (as written by the applicant)	It is estimated that 50 million Americans suffer from chronic pain, with patients relying mostly on opioids. In California, an estimated 45% of drug overdose deaths involved opioids in 2018. We are in dire need of new treatments for chronic pain. Although our first indication will be a rare painful condition, our gene therapy could potentially benefit other individuals with intractable painful conditions, as the gene we are targeting is involved in pain transmission and in many pain conditions.
Funds Requested	$3,997,149
GWG Recommendation	**(85-100): Exceptional merit and warrants funding, if funds are available**
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 85

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

Mean	84
Median	85
Standard Deviation	5
Highest	90
Lowest	70
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	9
(1-84): Not recommended for funding	5

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/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 **No:** 0	• The drug product has the potential to provide an improvement in the standard of care for the treatment of pain. • This is a gene therapy product to target SCNA disorders and treat chronic pain. There is an unmet clinical need based on failed treatment with opioids and addiction. The proposed product has the potential to target pain using a gene therapy approach to repress expression of a sodium channel and promote gain of function in patients with acromegaly, diabetic polyneuropathy and congenital pain disorders. • Inadequate treatment of chronic pain is an acknowledged problem globally. While this project target patients with a specific condition, it seems that the goal is to expand into multiple conditions that cause chronic pain. • This rare pain disorder targeted represents an unmet need. • The mode of action is novel. • If successfully developed, this approach could significantly impact treatment of chronic pain, specifically in pain that is associated with mutations in the sodium channel Nav1.7. The application is not entirely clear regarding what proportion of chronic pain suffers have this mutation. • The unmet need is too clear. However, the risk:benefit of the approach is not addressed.
GWG Votes	**Is the rationale sound?**
Yes: 12 **No:** 1	• The rationale appears sound for an AAV-based therapeutic. • There is strong proof of concept in published studies. • The rationale appears to be sound based on published literature showing proof-of-concept. • The rationale for targeting this mutation is clear.
GWG Votes	**Is the project well planned and designed?**
Yes: 12 **No:** 1	• The development of a potency assay is a strength. • While the timelines appear ambitious for chemistry, manufacturing and controls, the project should be achievable. Note that the coefficient of variation targets for assay qualification may be unrealistic for all biological assays. Assay readiness needs to be in place prior to testing at Month 8. • The plan for animal studies as presented in this application is well planned. However, the ability to accomplish this work in this time frame is uncertain. Equally important, this particular product hasn't been tested in vivo at all, so he ability to transition this to humans is very much dependent upon the safety of this approach in humanized mice and in a relevant preclinical model. • Overall, reviewers considered that there was not yet enough data to support funding.
GWG Votes	**Is the project feasible?**
Yes: 11 **No:** 2	• The timelines are quite ambitious; however, they are potentially feasible. • The project is feasible, but note that QC assay readiness needs to be in place prior to testing at Month 8 before toxicology batch manufacturing. • A panelist had minor concerns that the applicants have't yet had an INTERACT meeting. • The project failed to get an INTERACT meeting, and there were concerns raised as to the feasibility of the zinc finger target and potential for impact. • The CMC program was not adequately developed.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12 **No:** 1	• The investigators present significant discussion of sufferers of chronic pain and delve deeply into the diversity of that population. Although this application does not include humans, it would seem that this project will incorporate diversity. • All activities incorporate inclusion into the technical plans when appropriate. • This was considered adequate.

DIVERSITY, EQUITY, AND INCLUSION (DEI)

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

DEI Score: 7.0

Up to 7 patient advocate and nurse members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	0	*none*
6-8: Responsive	2	• There is adequate discussion on health disparities among people suffering from chronic pain. The applicant states that women tend to be diagnosed with pain disorders more; one attributing cause could be estrogen being linked to pain sensitivity. It's also suggested that females and racial/ethnic minorities experience longer wait times for treatment and receive lower opioid prescriptions. • The applicant will work with clinical research partners that offer training on implicit bias, on the basis of a study where an individual's pain can be perceived incorrectly or differently by other races, • In the future, the applicant plans to create recruitment materials in different languages, offer transportation, and cover childcare cost. They also plan on establishing a Race and Ethnicity Diversity Plan, collaborating with communities and advocacy groups to enhance outreach and provide education to increase awareness. • The application provides an adequate DEI plan.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-16262
Title (as written by the applicant)	Parkin Gene Therapy for Parkinson's Disease (PD)
Translational Candidate (as written by the applicant)	A gene therapy to deliver the Parkin gene to Parkinson's Disease (PD) patients
Area of Impact (as written by the applicant)	The candidate gene therapy will restore health to the cells that are dying of Parkinson's Disease (PD), restoring normal movement.
Mechanism of Action (as written by the applicant)	This gene therapy will restore health to the cells that are dying in Parkinson's Disease (PD). But restoring function to sick and dying cells, the proposed gene therapy will restore the normal homeostasis of dysfunctional brain circuits involved in movement to generate smooth, coordinated movement that normal individuals take for granted.
Unmet Medical Need (as written by the applicant)	There are no disease modifying therapies for Parkinson's Disease (PD). The candidate gene therapy targets the most common genetic cause of the disease, by providing a neuroprotective factor that can restore health to diseased cells. Our therapy has the potential to provide the first curative therapy for the movement disorder associated with PD.
Project Objective (as written by the applicant)	Conduct of a Pre-IND Meeting with the FDA
Major Proposed Activities (as written by the applicant)	• Assay Optimization and Rodent Efficacy Analysis in Dose-Response Studies • Dose Range Tolerability and Target Area Coverage in Non Human Primates • Pre-IND Meeting with the FDA
Statement of Benefit to California (as written by the applicant)	Parkinson's Disease (PD) is creating an increasing health burden to California at alarming rates. Even more alarming is the rate at which young people are getting diagnosed with PD. Our research will not only provide a novel, disease-modifying therapy, but it will remove research bottlenecks by defining useful biomarkers in animal models and developing assays that can translate to additional research programs for additional therapeutic development.
Funds Requested	$1,938,990
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	1
Highest	87
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: 13 **No:** 0	• The candidate is an AAV-based therapeutic for the treatment of Parkinson's Disease (PD), and could provide a disease-modifying option that would surpass the current standard of care. • There are currently no cures or disease modifying therapies for PD. • The product would accelerate or increase the likelihood of successfully developing a stem cell technology that significantly improves patient care. • Bi-allelic mutations in the Parkin gene are a rare, but severe, form of PD with early onset. Cures and treatments are desperately needed. • The applicant is developing a product for a disease with significant unmet medical need (PD). This application has potential to make a significant impact for patients.
GWG Votes	**Is the rationale sound?**
Yes: 13 **No:** 0	• The rationale is sound. The CMC plans appear to be appropriate for this stage. • The data support development of the product. • The overall rationale is sound. • The rationale for testing the approach in Parkin patients is clear and straightforward, but the rationale for expanding into additional PD patient populations is less clear.
GWG Votes	**Is the project well planned and designed?**
Yes: 13 **No:** 0	• The project appears to be sufficiently planned. • The project is well planned and designed both for preclinical and clinical development. • Overall, the project is well planned and designed. The only potential risk is the switch from one cell line to another cell line in the production method. It appears that all of the pre-clinical studies were conducted using the first cell line, but the subsequent product will be developed using the second cell line. The applicant does not have a risk mitigation plan that potentially accounts for this switch. • Some CMC plans were not fully developed. • Yes, proposed activities are essential to the project, and the timeline demonstrates an urgency that is commensurate with CIRM's mission.
GWG Votes	**Is the project feasible?**
Yes: 13 **No:** 0	• Yes, the project timelines are feasible for CMC. • The overall project is feasible. • The proposed team is appropriately qualified and staffed, has access to all the necessary resources to conduct the proposed activities, and has a viable contingency plan to manage risks and delay.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 10 **No:** 3	• This project does a good overall job of adhering and upholding the principles of DEI. • Aspects of DEI were not completely addressed. • DEI sections were not very detailed.

DIVERSITY, EQUITY, AND INCLUSION (DEI)

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

DEI Score: 5.0

Up to 7 patient advocate and nurse members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

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

response		
6-8: Responsive	0	*none*
3-5: Not fully responsive	2	• The applicant stresses that PD is considered a disease limited to well served groups, and are working to correct that misconception. Because of this, there is a disparity in treatment and diagnosis. The applicant focused on early onset Parkinson's and specifically in the African American population. However, the DEI section overall was thin. The applicant needs to elaborate more on how interactions with communities of color will inform trial design and other aspects of the project.
0-2: Not responsive	1	• No meaningful DEI plan.

Application #	TRAN1-16158
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)	IL-12-expressing Cargocyte is being developed to treat metastatic solid tumors.
Area of Impact (as written by the applicant)	Metastatic cancers have few therapeutic options. This product offers an effective treatment for late-stage cancer.
Mechanism of Action (as written by the applicant)	This product is a precision delivery therapeutic that seeks out metastatic cells, deeply penetrates the anatomical sites at which metastatic cells thrive, and locally produces an immune activating therapeutic, interleukin-12 (IL-12). This product minimizes toxicity that may occur in response to systemic administration.
Unmet Medical Need (as written by the applicant)	Powerful cytokines (such as IL-12) are toxic when delivered systemically due to the high concentrations required. Local delivery approaches to the tumor are ideally suited for minimizing toxicity. This product is designed to deeply penetrate tumors and locally synthesize IL-12, offering a safe and effective method for treating metastatic cancer.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Develop of a near-GMP process with quantitative control measures • Design a clinical trial addressing diversity, equity and inclusion using a decentralized clinical trial approach • Pre-IND meeting with FDA
Statement of Benefit to California (as written by the applicant)	The 'cargocyte' is an innovative platform and a vertical move for clinical science. Our company continues to grow our R&D team and will manufacture our near cGMP clinical product at our CA biotech facility. The proposed research will drive our manufacturing process and accelerate the growth of our organization by an expected 5 FTE (additional 40% growth in FTE) within 2.5 years.
Funds Requested	$3,196,087
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	81
Median	84
Standard Deviation	5
Highest	86
Lowest	70
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	6*
(1-84): Not recommended for funding	7

* See Minority Report below

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 11 **No:** 1	• The proposed 'Cargocyte' product is very unique and novel. The value proposition of the technology is low cost, local delivery of cytokines into the tumor, and the possibility of applying the technology in multiple oncology indications. • This is a revised, resubmitted application. The applicant significantly improved the application and responded to all the reviewer's comments from the previous submission. • The applicant has done a good job of addressing prior critiques from the Grants Working Group (GWG), which were largely related to design and feasibility and the applicant's heavy reliance on CROs for the manufacturing. The significance and potential impact are thus more clear in this resubmission. • The potential impact is the ability to deliver localized, short-acting cytokines to treat metastatic triple negative breast cancer (TNBC), which is difficult to treat due to a lack of actionable targets and therapeutic options. • The resubmission focuses on breast cancer. Advanced triple-negative breast cancer represents an unmet medical need due to poor prognosis and lack of therapeutic options.
GWG Votes	**Is the rationale sound?**
Yes: 9 **No:** 3	• The applicant has improved their scientific rationale and provided more data on the significance of IL-12. While it remains unclear that IL-12 is the best choice for immunotherapy of TNBC, the preliminary data support further development. • The applicant added more rationale for the use of IL-12 (the initial submission was centered around cargocytes), which improved the application. It remains a bit unclear whether IL-12 is the best option, and whether it has been chosen based on fewer competitors or potential efficacy. • Not enough preclinical data demonstrate (i) specific homing of cells to sites of tumor (and not to other inflammatory sites), (ii) ability to infiltrate a difficult-to-access tumor microenvironment, and (iii) ability to generate sufficient immune response to have clinical impact. • The biodistribution data do not provide sufficient evidence to suggest that TNBC cells home to tumors in other organs (besides the lung) in sufficient numbers to have a potential benefit. The ability to deliver a potentially therapeutic dose has not been shown. • The basis for the ability of cargocytes to penetrate dense stroma appears to be based on their design as enucleated derivatives of MSCs. However, experimental evidence demonstrating this ability was not identified. While they may localize to the tumors in the lungs, they would have to infiltrate the solid tumor to deliver the IL-12 and turn the 'cold' tumor microenvironment 'hot'. The only data related to this was from a microfluidics experiment, which does not simulate the complexity of a tumor environment.
GWG Votes	**Is the project well planned and designed?**
Yes: 10 **No:** 2	• The project appears well-planned and designed. • Added details regarding manufacturing steps and performance criteria included (i) a detailed protocol for enucleation and (ii) performance criteria including (a) enucleation efficiency, (b) impurity measurements, and (c) potency assays.
GWG Votes	**Is the project feasible?**
Yes: 11 **No:** 1	• The project looks feasible within the proposed timeline. • While feasible, the project appears very costly. The yearly lease for the clean room facilities seems exorbitant. • Importantly, a major change from prior submission is that manufacturing will now be completed entirely at the applicant organization, with no reliance on third parties for completion.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12 **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	1	• The applicant presents case rate data for the four major cancers across various ethnic groups. • The applicant states that some of the differences in cancer risk, incidence, and survival among people of different racial and ethnic backgrounds can be attributed to biological factors, but economic and social disparities also contribute to these differences. • The applicant states that Cargocytes can be mass distributed to any hospital or infusion center currently administering oncology therapeutics. They believe this to be a major technical equalizer in addressing access and availability to underserved communities. • The applicant states that as they advance into clinical trials they will seek to engage of wide-range of socioeconomic groups affected by indications under investigation. The applicant also plans to account for differential disease occurrence in their clinical trial design, participant population, and statistical analyses. • The applicant states they will generate a diversity recruitment plan as well as incorporate decentralized clinical (DCT) solutions in their trials to enable access, increase recruitment, and lower the burden of trial participation. • The applicant states they will work with participant recruitment agencies specialized in outreach to minority groups. • The applicant plans to evaluate the feasibility of recruiting community-based oncologists to partake in the clinical trials or partner with principal investigators to provide continuous support to participating patients. • The applicant will work to create easy accessibility to trial sites. • At the study design phase, the applicant will engage with patient advocacy groups and study sites to further refine their diversity recruitment and retention plan. • Lastly, they name an analytics platform that they will use to build a recruitment dashboard that reports recruitment rate and diversity in real-time, to adjust recruitment strategy in flight to ultimately include adequate participation of Black women in their clinical trials.
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.

Application TRAN1-16158 received a median score of 84, with seven Grants Working Group (GWG) panelists scoring 70 to 84 and six GWG panelists scoring 85 to 86. One supportive reviewer noted the "very unique and novel" nature of the proposed product and detailed the value proposition: low cost, local delivery into the tumor, and the possibility of expanding to multiple oncology indications. Another supportive reviewer noted the "lack of actionable targets and therapeutic options" for triple-negative breast cancer (TNBC).

The six GWG panelists in the supportive minority also commended the applicant's responsiveness to feedback from the prior GWG review, and noted that a major concern from the prior submission - the use of a CRO for manufacturing activities - had been resolved as the applicant is now able to and will conduct these activities in-house. The CRO-based manufacturing in the prior project plan had raised concerns about delays to the project timeline.

Reviewers generally agreed that uncertainty remains as to whether IL-12, the therapeutic molecule within the Cargocyte product, is the best possible therapeutic option for a triple-negative breast cancer (TNBC) immune therapy. Reviewer scoring in the non-supportive majority (less than 84) provided constructive feedback on this issue under Key Question 2, *Is the rationale sound?* Supportive reviewers, in contrast, thought the current preliminary data adequately support further development and the project therefore warrants funding at this time.

Application #	TRAN1-16025
Title (as written by the applicant)	Translating iPSC-derived Thymic Epithelial Cells into a Cell Therapy for Children with Congenital Athymia
Translational Candidate (as written by the applicant)	Functional and patient HLA-matched thymic epithelial cells (TECs) derived from induced pluripotent stem cells (iPSCs)
Area of Impact (as written by the applicant)	To provide HLA-matched rescue of T cell immunodeficiency in patients with congenital athymia
Mechanism of Action (as written by the applicant)	Transplant of the proposed candidate will restore thymic function in athymic patients
Unmet Medical Need (as written by the applicant)	Currently available treatment is allogeneic cultured thymic tissue transplantation using HLA-unmatched thymic donor tissues transplanted into a patient. However: 1. tissue availability is scarce, 2. treatment in the US is only available at one site, 3. HLA-unmatched can lead to poor graft function necessitating continued isolation and causing a near 100% incidence of autoimmune complications, some of which are life threatening.
Project Objective (as written by the applicant)	pre-IND meeting
Major Proposed Activities (as written by the applicant)	• generate patient specific HLA-matched iPSCs • generate TECs from HLA-matched iPSCs • demonstrate T cell immune reconstitution and functional immune response in an athymic mouse model
Statement of Benefit to California (as written by the applicant)	In addition to congenital athymia patients, many others could benefit from restored thymic function, providing economic benefit to California by decreasing societal costs: 1. allogeneic HSCT recipients (>2000/year in CA) who are exposed to numerous thymic insults. 2. cancer patients (>200,000 new cases/year in CA) receiving immunotherapies that require functional immune system, 3. solid organ transplants (~5,000/year in California) to induce tolerance and diminish lifelong immunosuppression.
Funds Requested	$5,880,903
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	81
Median	80
Standard Deviation	3
Highest	85
Lowest	75
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	1
(1-84): Not recommended for funding	12

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 11 **No:** 0	• Congenital athymia is a life-threatening disorder defined by absence of thymic development and profound T cell immunodeficiency. The only currently available treatment is allogeneic cultured thymic tissue transplantation, but it's not always effective due to limited donor thymus tissues, poor graft function and autoimmune complications. Thus, there is a critical need for better treatment options. • Congenital athymia is a rare disorder, with about 17-24 new diagnoses per year in the US. Standard of care, thymic transplant, has significant limitations. The advantage of this strategy over current treatment is in the derivation of HLA-matched allogeneic cells. • This application aims to derive functional HLA-matched thymic epithelial cells (TECs) from induced pluripotent stem cells (iPSCs) into a cell therapy for congenital athymia. It would be a fantastic iPSC-derived cell therapy example, if successful. • Current treatment by thymic transplant costs $2.7M. Palliative care for infections and autoimmune complications results in mean 3-year economic burden per patient of >$5.5M. Some patient care may rise to almost $10M over 3 years. If the proposed therapy is successful, it will also likely have a high price, but it will be more likely to have beneficial impact on patients. In addition, over the patient's lifespan, it could result in reduced health care intervention and cost due to prevention of infectious disease and autoimmune complications. • The team addresses a critical unmet need for this rare group of patients.
GWG Votes	**Is the rationale sound?**
Yes: 9 **No:** 2	• The team is building on a series of studies. Using single cell transcriptomics, they derived an understanding of the regulatory networks and differentiation pathways involved in differentiation of thymic epithelial stroma from the fetal anterior foregut. From these studies, they inferred that cytokine and other lymphoid signals are mediators of maturation of TECs. They've converted this knowledge into a reproducible differentiation platform to generate thymic epithelial progenitor cells (TEPCs) from iPSCs. The intention is that TEPCs will differentiation into TECs in vivo after interaction with the lymphoid niche. • Using two mouse models of athymia, the applicants performed proof of concept studies of five different hiPSC lines in 15 animals. They demonstrated reproducible generation of primary thymic tissues and progression of thymocyte differentiation from double negative, to double positive, to single positive with TCR rearrangements. • The team provided data for the differentiation platform that derives functional TECs from hiPSCs or hESCs. They provided data that transplanted iPSC-derived TEC organoids into an athymic humanized NSG-Foxn1-/- model and demonstrated human T cell immune reconstitution with no immune complications, using using two different ESC and four different iPSC lines. They therefore propose to progress this protocol toward clinical translation by generating in vitro-derived TECs for patients with congenital athymia using HLA-matched iPSCs. • Regenerating thymic epithelial function, such as through iPSC-derived TECs, holds great therapeutic promise. Extrapolating from the HLA-unmatched allogeneic thymus transplantation experience and the adverse events, the team reason that HLA-matched iPSC-derived TEC transplantation could be a safer and potentially more effective curative cell therapy for patients with congenital athymia than the standard of care. • The use of HLA-matched cells to replace thymic function is reasonable. • There is a lot of concern about whether the proposed approach can be suitable for many patients because of the lack of iPSC lines which would be needed to match patients. • Applicants need to explain how HLA "matching" will work.
GWG Votes	**Is the project well planned and designed?**
Yes: 8 **No:** 3	• Concerns were raised during the review regarding the quality of various reagents used at different steps of the product manufacture. The PI's responses to the questions adequately addressed these questions. • Generally, the project is well-planned and designed, with one caveat regarding the HLA matching. • There is some confusion about whether the term "HLA-matched" is accurate. The PI needs to define to what extent an HLA match would be needed to go forward with making iPSCs from a donor. For example, would 3/6 be sufficient, would 5/6 be sufficient? Concern is that it's unlikely to find a 100% matched donor. • It's very reasonable for the team to move toward this project towards clinical translation.

	However, the reason for generating 3 new "HLA-matched" iPSC lines is not clear. It's unclear who the HLA will be matching. The team needs to prove the benefits of the proposed 3 new HLA-matched iPSC lines. • More clarity on the degree of HLA-matching between the cell product and the prospective patient is required. • The proposal has limitations related to HLA matching and cell purity.
GWG Votes	**Is the project feasible?**
Yes: 9 **No:** 2	• The project is likely to be achieved. TEC differentiation ability and variation from the newly generated iPSC lines present high risks. • A major concern regarding feasibility lies in finding a truly 100% HLA-matched donor for each of the subjects for the Phase 1 clinical trial. • Aside from HLA matching, the feasibility of generating the iPSC and differentiated TEC is less of a concern. However, the differentiation protocol is quite complex, and there may be challenges when scaling this up, including challenges sourcing all the factors of sufficient quality. • The reproducibility of differentiation has not been demonstrated. It needs to be provided with quantitative metrics across lines and batches. • Quality standards seem difficult to implement, and culture conditions are overly complex.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 11 **No:** 0	• The PI is already well-connected to the primary patient advocacy group, and will be presenting at an international meeting of advocates and families with 22q11.2 deletions. In addition they are undergoing training to identify implicit bias and learn debiasing techniques. They are hosting webinars for the two relevant foundations. Finally, they are also creating an advisory panel to engage patients, caregivers, key opinion leaders to developed trust in the community. • Currently the only therapeutic option, RETHYMIC, costs $2.7M with variable outcomes due to HLA-mismatching, and uncertain insurance coverage, and is only provided at one site. The proposed product addresses these gaps by developing an HLA-matched TEC transplant that could be used in any ethnic group by using the National Donor Marrow Program to source the iPSCs. NDMP has >9million donors with 41% from racial and ethnically diverse donors. • The team proposed to generate 3 iPSC-derived TEC products for three ethnically diverse patients with congenital athymia. The cell therapy would benefit congenital athymia patients worldwide. • This application upholds 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: 8.0

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	2	• The application presents a well-described DEI plan. • The applicant institution has a strong track record related to patient diversity. • There has been a consistent outreach effort with the congenital athymia patient population. Specific outreach through the two disease-specific foundations provides well managed partnerships that ensure patient identification and participation in a future clinical trial. • The lead investigator and the team have cultivated extensive outreach

		and are actively engaged in strategic alliances with physicians, NBS programs, patients, and families in California and beyond. They identify children with congenital athymia and provide expert care. • While demographic data was provided, there is a very limited ability to assess patient diversity due to the very rare incidence of this disease in the range of 20 people per year in the United States.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-16264
Title (as written by the applicant)	Advancing Next Generation CAR-T Cells for Renal Cell Carcinoma
Translational Candidate (as written by the applicant)	CAR-T with multiple gene enhancements, evolved to effectively and safely kill solid tumors. The CAR-T is against a unique target for kidney cancer.
Area of Impact (as written by the applicant)	Current CAR-Ts can not penetrate, proliferate, persist and effectively kill solid tumors. We used unbiased evolution to discover CAR-Ts that can.
Mechanism of Action (as written by the applicant)	Our gene-enhanced CAR-Ts, if safe and effective, could become 'one-and-done' therapy option for patients with kidney cancer. Given that we find our gene enhancements are universal and help many CAR-Ts (against other cancer types), this technology may have wider applications against many cancers.
Unmet Medical Need (as written by the applicant)	Currently cures against metastatic solid tumors, including kidney cancer, are rare. Our proposal evaluates our gene-enhanced CAR-Ts in kidney cancer. Our hope if to find safe and effective 'one-and-done' therapy for this cancer. If successful, our aim is to use this type of technology to discover gene-enhanced CAR-T against other cancers.
Project Objective (as written by the applicant)	To develop data package for a pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Pharmacology, pharmacodynamic, and pharmacokinetic studies • Cell production and manufacturing • Safety studies
Statement of Benefit to California (as written by the applicant)	Curing most solid tumors following metastasis is rare. Although CAR-Ts can cure patients with liquid tumors, multiple roadblocks exist in solid tumors. We used unbiased cell evolution principles to discover genes that substantially improve CAR-T efficacy in solid tumors. Our clinical product has multiple gene enhancements and shows promising preclinical benefit. We will test our novel CAR-T first in kidney cancer. If successful, we aim to use this technology in other solid tumors.
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	78
Median	80
Standard Deviation	3
Highest	85
Lowest	72
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	1
(1-84): Not recommended for funding	12

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 9 **No:** 2	• If the development of the proposed product is successful, this product may address the shortcomings of the current CAR-T cell therapy approach, which usually uses single targets, and has limited efficacy in solid tumors. Identification of potential genetic targets to boost T cell responses would significantly improve efficacy of cancer cell therapy products. • While cellular therapies for solid tumors have had limited success thus far, preclinical data presented in this application support the development of a unique autologous T cell therapy for metastatic renal cell cancer (RCC). • There is concern for toxicity to the normal renal cortex.
GWG Votes	**Is the rationale sound?**
Yes: 8 **No:** 3	• This autologous CAR-T approach is supported by substantive preliminary data included in the application. This includes identification of a novel target antigen expressed on RCC and the development of high affinity protein specific for this antigen. This also includes genetic modification of the CAR vector to enhance cytolytic activity and promote signaling without terminal differentiation and exhaustion. • The project rationale is scientifically sound, specifically the proposed CMC development program. However, additional information to support the development and manufacturability of the product may further support the project rationale, including proposed controls that will be in place to ensure consistency and quality product manufacturing. • There are some concerns about efficacy and where the actual work would be done.
GWG Votes	**Is the project well planned and designed?**
Yes: 4 **No:** 7	• The CMC development of the product is well-planned, including milestones and planned interactions with regulatory authorities. • Proposed testing for efficacy and safety will primarily rely on in vivo studies in immune deficient mice implanted with human RCC tumors. Unfortunately, these models are not always predictive of efficacy and safety in humans. Orthotopic human tumors derived from cell lines do not recapitulate the immunosuppressive TME of human tumors in vivo. Potential on-target off-tumor toxicities are also difficult to evaluate in mice lacking expression of the human gene target in any normal tissues. • Restricted RCC specificity has been tested using a CAR Cell Microarray assay. While these results may be accepted by the FDA, this test may not be sufficient to detect target protein expression in normal tissues and predict on-target off-tumor toxicities. In this case, this may not sufficiently exclude toxicity to normal kidney cells. • The procedure for manufacturing autologous CAR-T cell product includes the several sequential steps: selection of CD4/CD8 T cells; T cell activation, electroporation/gene editing; viral transduction; and expansion. The resulting product may contain T cells that are gene edited only, transduced only, gene edited and transduced, and neither gene edited nor transduced. Each of these product subsets will have different functions and it may be necessary to develop assays to quantify each of these product subsets in the final product. This will also be necessary to define the dose of the intended cells in each product. • The assays are not well described. Experiments are mostly not done in California and are sourced out - the location of activities is not clear.
GWG Votes	**Is the project feasible?**
Yes: 9 **No:** 2	• Many of the proposed preclinical studies will be carried out by a contract manufacturing organization. This large multinational company has extensive experience in this work as well as in the manufacturing of cellular products for a clinical trial. • The project as proposed seems feasible. However at this stage of product development, very limited data are available regarding the development and manufacturability of the product. • There were some minor concerns that the timeline was too ambitious. • The applicant has laboratory locations in California and out of state, and some of the proposed work will be carried out with a contractor. The amount of work carried out in California is not clear.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 11	• RCC is known to disproportionally affect Hispanic and Black populations. • Development of an effective cellular therapy would benefit minority populations in California, but this treatment will likely be very expensive and this may limit access in the

No: 0	same populations.

DIVERSITY, EQUITY, AND INCLUSION (DEI)

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

DEI Score: 7.0

Up to 7 patient advocate and nurse members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	0	*none*
6-8: Responsive	1	• Adequately defined DEI plan.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-16217
Title (as written by the applicant)	Targeting triple-negative breast cancer by novel CD4 TCR-engineered T cells
Translational Candidate (as written by the applicant)	HLA-restricted *[antigen redacted]*-specific TCR-engineered CD4+ T cells
Area of Impact (as written by the applicant)	Advanced or metastatic triple-negative breast cancer (TNBC) patients who failed to respond to immune checkpoint therapy or prior various treatments
Mechanism of Action (as written by the applicant)	TNBC patients poorly respond to immune checkpoint therapy, and TNBC remains an unmet medical need. *[Antigen redacted]* is highly expressed in more than half of TNBC patients. The mechanism of action is that *[antigen redacted]* specific CD4+ TCR T cells directly kill tumor cells through antigen recognition and indirectly kill tumor cells through recruitment of other cells, thus generating potent and long-lasting antitumor immunity.
Unmet Medical Need (as written by the applicant)	TNBC is the most aggressive subtype of breast cancer and has few treatment options. Furthermore, TNBC patients respond poorly to immune checkpoint therapy . Thus TNBC still remains an unmet medical need. Our proposal is to develop novel CD4+ TCR T cells for TNBC patients with high expression of *[antigen redacted].*
Project Objective (as written by the applicant)	Pre-IND meeting with FDA
Major Proposed Activities (as written by the applicant)	• To generate GMP grade Master and Working Cell Banks and viral particles (supernatants), and certificate testing • To complete nonclinical studies (biodistribution and toxicity), and scale up production of CD4 TCR-T cells • Regulatory and clinical protocol development and Pre-IND meeting with FDA
Statement of Benefit to California (as written by the applicant)	Breast cancer is the leading cause of death for women in California and in *[county redacted],* which is one of the most racially and ethnically diverse regions in the US. Among different subtypes, TNBC is the most aggressive subtype of breast cancer, with few treatment options and remains an unmet medical need. There are alarming racial/ethnic disparities in breast cancer outcomes in our catchment area. Thus, the proposed study will benefit the state of California and this county.
Funds Requested	$3,992,917
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: 78

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

Mean	76
Median	78
Standard Deviation	5
Highest	83
Lowest	70
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 9 **No:** 2	• Yes, there is a significant unmet medical need for novel therapies for triple-negative breast cancer (TNBC). • The project will have an impact on breast cancer therapy. • The overall concept is good, but the target product profile (TPP) is confusing. • Yes, TNBC is a very aggressive form of breast cancer with poor prognosis and high relapse rate; the proposed therapy could potentially impact treatment options for many women.
GWG Votes	**Is the rationale sound?**
Yes: 9 **No:** 2	• The overall rationale is sound. The major weakness relates to potential cross-reactivity and toxicity associated with the TCR-based construct. The applicant had done limited work to demonstrate lack of cross-reactivity for peptide sequences homologous to *[antigen redacted]*. • Yes. However, some preliminary studies used non-related constructs; the rationale behind using these was not clear. • While the rationale is sound, the incremental value of the various design elements that are part of this therapeutic has not been tested in a systematic way. Sometimes an element is tested in a CAR instead of a TCR, sometimes with non-TNBC tumors. • There are problems with the TPP. The applicant may not have understood how to put it together, or have forgotten to finalize it. • The preliminary data in the proposal do not convincingly show reproducible disease modifying activity in the target indication with the actual candidate.
GWG Votes	**Is the project well planned and designed?**
Yes: 5 **No:** 6	• Safety concerns are poorly addressed in this proposal. • Omitting control T-cell biodistribution in tumor-bearing mice does not make sense. • In terms of CMC, the applicant seems to be using dated manufacturing techniques that could make the product susceptible to contamination. For guidance, see https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9815724/ • The most parsimonious answer is "partially". There was a disconnect between the pilot nature the toxicology study and the budget for this study, where it appears as a GLP study. If the study will be conducted under GLP, the assumption is that it would be IND-enabling toxicology. There is no clear plan for pilot dose studies. IND-enabling studies with CAR-Ts tend to be hybrid in design (pharmacology and tox), so perhaps it would make sense to tighten the pharmacology aspect first.
GWG Votes	**Is the project feasible?**
Yes: 10 **No:** 1	• Overall the project is feasible, but has some risk related to potential cross-reactivity of the TCR construct. • Many of the preliminary data provided are not directly relevant to the actual candidate. • The project appears potentially feasible, but it needs a more clearly defined, stepwise approach.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 11 **No:** 0	• The applicant articulated an understanding of DEI and, specifically, will endeavor to include patients of diverse backgrounds in the planned clinical trial. • The future trial will be initiated and conducted through the collaboration with a large academic medical center located in one of the most racially and ethnically diverse regions in CA. • Yes, the project upholds 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: 8.0

Up to 7 patient advocate and nurse members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	0	*none*
6-8: Responsive	1	• Part 1: An overview of the incidence of breast cancer among different ethnic groups is presented. To ensure diversity, equity, and inclusion in their project, the applicant plans to incorporate factors such as race, ethnicity, sex, gender, and age in their study design. • Part 2: The applicant describes biologic differences among different ethnic groups, and describes disparities in access to care. Because of the restricted expression of *[antigen redacted]* and the use of TCRs with improved function and safety, the applicant believes that their candidate therapy could cover a broad and diverse population of breast cancer patients. • Part 3: The applicant states that they will take advantage of their partner academic medical center's strategic plans and policies to develop their DEI enhancement strategies. The applicant team will disseminate their cancer research findings to community residents through their partner university's community-based hub.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN4-16067
Title (as written by the applicant)	Microfluidic iPSC-derived organoids for high-throughput therapeutic development and drug evaluation
Translational Candidate (as written by the applicant)	iPSC-derived tissue organoids for drug screening
Area of Impact (as written by the applicant)	High-throughput patient-derived preclinical models for pharmaceutical drug development to fulfill the vision of FDA Modernization Act 2.0
Mechanism of Action (as written by the applicant)	The microfluidic iPSC-derived organoid technology is compatible with conventional 3D culture based high-throughput screening platform, so it can be easily adopted by pharma, biotech companies, and academic labs and core facilities to become the workhorse for therapeutic discovery and development.
Unmet Medical Need (as written by the applicant)	A high-throughput, cost-effective iPSC-derived organoid screening platform with a library tissue models from diverse sources that provide population diversity
Project Objective (as written by the applicant)	Deployed at pharma, academic, and CRO partner site
Major Proposed Activities (as written by the applicant)	• Microfluidic establishment of a library of iPSC-derived 3D tissue organoids recapitulating population diversity • Automation with an integrated microfluidic device to enhance throughput and user experience • MIO assay development, MIO characterization, and MIO library establishment
Statement of Benefit to California (as written by the applicant)	The MIO technology will enable the first high-throughput therapeutic screening platform with iPSC-derived organoids, providing pharma and biotech companies in California with a distinct competitive advantage given FDA Modernization Act 2.0. It will also lead to formation of a new company that generate revenue, employment, and tax dollars for California. The MIO library will capture population diversity, including minority and underprivileged groups underrepresented in typical clinical trials.
Funds Requested	$1,287,634
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	2
Highest	77
Lowest	70
Count	12
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	12

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 9 **No:** 1	• Yes, there is clear evidence that there are situations where the 3D environment of a disease state is best recapitulated in an organoid, but the screening of potential therapeutics in organoids is hampered by the reproducibility of organoids and their adaptability to high content screens. If this proposal is successful, the diverse iPSC organoids would improve the ability to understand screening outcomes in a broader range of patients. • The fact that the applicants have already created a library of diverse iPSC is a strong positive of this application. • The applicants have provided a lot of data showing a number of different types of organoids that have been successfully generated. • Advances in iPSC organoid manufacturing could accelerate drug discovery. • Applicant proposes to build an innovative, fully automated emulsion microfluidics device that allows high-throughput generation of iPSC-derived organoids compatible with automated imaging-based screening platforms. If successful, this would address unmet need for effective and quick drug screening. • Landscape of already accessible devises is not well described - i.e why is this system superior to other systems? Generic description of concepts makes it difficult to understand the specific value of the product.
GWG Votes	**Is the rationale sound?**
Yes: 2 **No:** 8	• It is clear that organoids can be critical to understanding disease progression and treatment. For them to reach their potential, there is a strong need to overcome batch variability in organoid generation. This application attempts to address this by making the organoids via a microfluidic approach. • It is hard to judge more fully because there are so few details on the microfluidics approach. • The use case for the technology is not clear. The advance over state-of-the-art technologies is not argued in a convincing fashion. • The rationale of using organoids as substitutes for drug screening is not novel and does not differentiate the product from already existing products. • The applicant states that other commercially developed microfluidic droplet generators are not suitable for the application and lack the integration of multiple processes that are required - however, their product does not address this problem. • The applicant needs to better demonstrate that their organoids will actually reflect clinically relevant situations and be predictive enough for useful drug evaluation/selection.
GWG Votes	**Is the project well planned and designed?**
Yes: 2 **No:** 8	• The applicant plans to advance a novel FDA, CLIA, and IVDR-compliant medical device that can rapidly grow iPSC-derived micro-organospheres (iPSC-MIO). • The technology is proprietary but some general details are provided. • Criteria for success are provided. • The project plan is difficult to judge due to lack of details. • The metrics for success need to be quantitatively defined for the end organoid products.
GWG Votes	**Is the project feasible?**
Yes: 5 **No:** 5	• The applicant generates an organoid "Village" platform to study diabetes, which will be adapted to the new approach. • iPSC libraries are in place and differentiation protocol are established. The microfluidics system is in place. • Feasibility of iPSC-based GWAS has been demonstrated. • The proposal has limited preliminary data on organoids, • The team is well qualified and staffed. It is clear that the people on the project have the necessary experience and have achieved similar goals in the past. • Without more details, the feasibility of the project is hard to judge. • iPSC differentiation may be difficult in the MIO droplets. This was not robustly demonstrated.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 10	• The iPSC library in the proposal is from a diverse population and their use in drug screening helps ensure effects of a particular drug are the same on underserved populations as they are on the white population. • The project upholds principles of DEI. • Central to the innovation is an extensive library of iPSCs and their derived MIO models.

No: 0	These represent a mosaic of genetic diversity and thus mirror the complexities of real-world patient populations.

DIVERSITY, EQUITY, AND INCLUSION (DEI)

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

DEI Score: 8.5

Up to 7 patient advocate and nurse members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	1	• The platform, if it were to be successful, could accelerate research and broaden patient / ethnicity impact and could be a great benefit to patient DEI in that regard. • It is designed for high-throughput screening of iPSC-derived tissue organoids. Such an approach could generate a library of microfluidic iPSC-derived organoid (MIO) models of different tissue types, diseases, and human ancestry. • The product is a possible avenue for mitigating healthcare disparities rooted in the underrepresentation of diverse populations in clinical trials.
6-8: Responsive	1	• Adequate DEI response.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-16162
Title (as written by the applicant)	Translation of pan-cancer immunotherapy by GlyTR2 CAR T cells
Translational Candidate (as written by the applicant)	GlyTR2 CAR T cells
Area of Impact (as written by the applicant)	Refractory/metastatic solid cancer
Mechanism of Action (as written by the applicant)	T cell directed killing of cancer cells by binding abnormally expressed carbohydrate antigens.
Unmet Medical Need (as written by the applicant)	Treatment of non-resectable recurrent/metastatic solid cancers is currently palliative only. Available systemic treatments fail to eradicate disease and typically delay disease progression by only months, with patients quickly becoming refractory. Thus, the prognosis remains abysmal for patients with advanced solid tumors and there is an urgent unmet need for novel mechanisms of action and additional paradigm shifting therapeutic options.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Chemistry, Manufacturing & Controls • Pilot Pharmacology, Dose-Finding Studies, Pilot Safety Studies • Regulatory & Clinical Strategy
Statement of Benefit to California (as written by the applicant)	Development of a novel pan-cancer therapy for patients with refractory/metastatic solid cancers.
Funds Requested	$4,598,304
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	7
Highest	82
Lowest	60
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 8 **No:** 4	• The proposed pan-cancer immunotherapy using GlyTR2 CAR T cells will have a great impact on the treatment of different types of cancers including solid cancers, given the limitations with current CAR T cell therapy to treat solid tumor cancers. The proposed GlyTR2 CAR T cell can target multiples tumor-associated carbohydrate antigens (TACA's) that are present in nearly all cancer cells and have limited to no expression in normal tissues. • The proposed CAR T cell product to target various metastatic/refractory tumor types with high avidity has the potential to be impactful based on the proof-of-concept data presented. The proposed product has the potential to highly impact an unmet clinical need for multiple refractory/metastatic solid tumors. However, its is unclear that the "pan-cancer" approach will be acceptable to FDA and this will need to be discussed either by INTERACT or pre-IND prior to launching a significant CMC program. • Using a pan-cancer targeting moiety makes this application non-focused as this may attack indiscriminately. The produced CAR-T cells may target cells that bind carbohydrates, such as endothelial cells. • Need to narrowly define target patient population.
GWG Votes	**Is the rationale sound?**
Yes: 7 **No:** 5	• The project rationale is sound and is supported by limited data provided in the application. In vivo studies should have been generated using a variety of cancer cell types to support the applicability of the pan-cancer product for the treatment of various cancer types. • Targeting carbohydrate antigens is a new idea. • Off-target effects on other endothelial cells are not considered. • Technically the milestones presented within the application are sound but there are some concerns. Given that the clinical indication is a "pan-cancer" approach designed to treat patients with several types of cancer, e.g., breast, ovarian and others with refractory/metastatic disease, it is important to obtain feedback from FDA on the acceptance of the intended clinical design and scope of the clinical plan. This will enable a focused plan on patient number, dose, dosing regimen and treatment strategy. The intention is to confirm that the intended "pan-cancer" clinical plan will be acceptable prior to manufacturing a complex CAR T product. • With respect to nonclinical testing, the plan is to consult with a company on the nonclinical testing strategy to presumably include dose-range finding, route of administration and devise a plan for assessing toxicity of the product. Again, it is suggested that the proof-of-concept data is packaged for an INTERACT or pre-IND meeting at this juncture to ensure the FDA is aware of the plan and can provide feedback. The questions should address FDA willingness to consider the "pan-cancer" basket clinical approach and provide a strategy for nonclinical testing. This, overall, should enable the CMC to proceed to scale the product accordingly. • Need to define non-clinical plan. • Insufficient preliminary data.
GWG Votes	**Is the project well planned and designed?**
Yes: 5 **No:** 7	• The proof-of-concept data are very compelling and robust in in vitro and in vivo models indicating potential to treat TACAs within different tumor types. However, there is no further strategy presented with respect to nonclinical or clinical development that would inform a pre-IND. Therefore, the seeking regulatory feedback on the "pan-cancer" clinical approach is highly recommended. • From the CMC development perspective, the project is well planned. The proposed development milestones including proposed interactions with regulatory authorities are reasonable. While the plan for the manufacturing of the project was provided, it was not clear what testing will be performed to assess the quality of the product and ensure the manufacturing consistency. • Concern over the pan-cancer design; may be better off focusing on a specific cancer.
GWG Votes	**Is the project feasible?**
Yes: 8 **No:** 4	• Pan-cancer designed might be a problem for FDA approval. • Based on the proof-of-concept data presented and the robust CMC plan, the project appears feasible. The main caveats relate to the absence of nonclinical testing strategy and whether the clinical approach will be acceptable. The feasibility and product plan should be discussed prior to embarking on a comprehensive CMC development program. • As described the application, the project seems feasible from the CMC perspectives. As stated earlier, preliminary data provided support further development of the project and the

	proposed milestone timeline seems reasonable. • Concerns that the product will be very difficult to generate.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 1 **No:** 11	• There was insufficient information presented to indicate that DEI had been adequately considered. The references that were provided need to be fully addressed and explained. • Not enough/detailed information regarding the inclusion of diversity in the project planning. • Not well-addressed in the application. • Needs more work.

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: 2.0

Up to 7 patient advocate and nurse members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	0	*none*
6-8: Responsive	1	*none*
3-5: Not fully responsive	0	*none*
0-2: Not responsive	2	• Inadequate response to the DEI section.

Application #	TRAN2-16130
Title (as written by the applicant)	Organoids Derived from Circulating Cancer Stem Cells for Drug Screening and Longitudinal Non-invasive Monitoring of Cancer Progression
Translational Candidate (as written by the applicant)	Organoids derived from circulating cancer stem cells
Area of Impact (as written by the applicant)	Solid tumors
Mechanism of Action (as written by the applicant)	Organoids originating from circulating cancer stem cells offer a unique avenue for assessing drug sensitivity, providing insights not only for the primary tumor but also for metastasized tumors. By replicating the unique cellular characteristics of tumors, these organoids provide a realistic model for drug response evaluation.
Unmet Medical Need (as written by the applicant)	While more anti-cancer drugs are now available, determining the optimal initial treatment and identifying the appropriate juncture to alter the treatment in the face of emerging resistance pose significant challenges. Achieving proper selection of the initial treatment and implementing efficient monitoring to detect resistance are critical unmet medical needs, therefore, advancements in precision medicine are needed to fully realize its potential benefits in cancer treatment.
Project Objective (as written by the applicant)	Start a LDT in a single CLIA lab
Major Proposed Activities (as written by the applicant)	• Optimize the organoid cultivation process from circulating cancer stem cells • Deep characterize the circulating cancer stem cell-derived organoids • Compare the clinical utlity by comparing to ctDNA measurement
Statement of Benefit to California (as written by the applicant)	This organoid platform offers California's solid cancer patients two crucial advantages. Firstly, its non-invasive blood sample collection surpasses biopsy-based screening, reducing healthcare disparities and enabling longitudinal monitoring. Secondly, it enables more effective drug screening. This suits to California's diverse population by detecting individual variations in drug responses, replacing decisions solely based on clinical trial results not representing the state's racial diversity.
Funds Requested	$1,204,875
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: 68

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	65
Median	68
Standard Deviation	5
Highest	70
Lowest	55
Count	12
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	12

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 6 **No:** 4	• The goal of this project is to leverage a successful technology that was developed by another company and licensed by the applicant company for the US market. This device selectively cultures circulating tumor cells (CTC) into organoids, with hopes of improving anti-cancer drug testing. • Currently, oncologists often resort to a best-guess approach based on their limited patient encounters and anecdotal insights. At the same time, literature reports provide outcomes with extended follow-up periods, rendering them less applicable to real-time decision-making. • The goal of this project is to advance precision medicine, with the plan to validate the process from organoid cultures to drug screening and implement it in a single CLIA lab. This will allow initiation of clinical validation from being able to test cancer patient samples to inform optimal treatment decisions made by oncologists. • CTC culture as organoids could revolutionize precision medicine methodology. • The role of circulating cancer stem cells (cCSCs) in cancer is evident, yet few current therapies account for them and having a streamlined approach to isolating and testing in a single CLIA lab could provide significant therapeutic advances. This application is a novel approach to isolating cCSCs from a small blood draw and then using a patented technology to generate organoids for drug testing. If successful, the outcome of this project would significantly improve patient care as it would provide therapies targeting the cCSC not just existing tumors. • The project is too broad and not enough detail is provided to judge the likelihood of success. Specifically, there needs to be a focus on 1 or 2 tumor types and more details need to be provided on strategies for organoid prep and culture, drug screening, detecting cellular outcomes and quantitating organoids made from cCSCs. • Understanding if blood can be stabilized through PBMC isolation and cryopreservation is also important in broadening the number of patients that can be reached using this kind of approach, but more detail needs to be given to understand the likelihood of this proposal having a significant impact. • Not clear that circulating cancer stem cell organoids will be useful predictors of drug sensitivity.
GWG Votes	**Is the rationale sound?**
Yes: 4 **No:** 6	• A significant weakness of this proposal is the lack of preliminary data and the lack of details on the scientific approach to meeting each step in their project plan. The only data shown are an image showing that organoids can be cultured, a figure showing cell viability after drug treatment, and expression of CSC markers in organoids. • The proposal lacks sufficient information to understand how robust this approach actually is. This is because the information provided is far too limited. • The relationship with the original inventor is unclear (extending even to the absence of a letter confirming the nature of the interaction). • There are multiple important goals that need to be achieved to make this a viable effort, and information on them is either minimal (in respect to detailed plans) or missing entirely. • The applicants give a few examples of places where this project could fail but provided limited contingency plans. • There is no alternative vendor for the culture plates and medium if manufacturing issues arise, resulting in potential delays in development and clinical testing. • The approaches for stabilizing the viability of the cCSC during shipment and organoid growth within the product need to be determined. • The applicant states that conducting clinical trials to obtain FDA approval is beyond their current scope and means. Their plan is to seek a partner to co-develop this product through clinical trials and market approval. • The cells they are growing are devoid of the tumor microenvironment, a limitation that is not considered. • The applicant should pick a specific disease and further demonstrate proof of concept and value.

GWG Votes	Is the project well planned and designed?
Yes: 1 **No:** 9	• Well planned and designed, but more information on company involvement is needed. • There is no information on regulatory interactions with the FDA. While this is not a requirement for funding, it would be helpful if the applicants described more about their plan for moving the diagnostic into a CLIA environment. The current plan is vague. There is discussion about validating the resulting assays, but again, no details. • Insufficient information on the project plan is provided.
GWG Votes	**Is the project feasible?**
Yes: 2 **No:** 8	• More preliminary data to substantiate the premise would be preferable. • The timeline presented in the Milestones section of the proposal does not match the timeline Gantt chart well. The animal studies referenced in the Gantt chart do not seem to be referenced in the Milestones. • The information on the team is not detailed enough. The team biosketches suggest that the team is well qualified, but this should have been explicated in the team organization portion of the proposal. • The resources and environment section is not sufficiently detailed for evaluation. • Collaboration letters are missing. Preliminary data to substantiate claims are missing.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 8 **No:** 2	• The applicant points out the higher incidence rate of some cancers among non-white populations, and notes that through the use of the proposed organoid model outcomes for under-represented patients may be better understood. • The Principal Investigator for this project serves as a board member for the *[cancer care foundation name redacted],* demonstrating commitment to enhancing cancer education, particularly for first-generation immigrant patients facing language barriers. • The PI is an oncologist with a long history of interacting with Asian cancer patients, who recognizes the fear some patients feel towards tumor biopsies. The PI, fellow oncologists on the board, and volunteers have provided valuable insights into the potential adoption of the organoid platform by oncologists and its acceptance among a diverse group of patients. • Outreach to underserved populations is described only for Asian patients. The applicant also discusses language barriers, and fear of tumor biopsy among underserved groups. • Though the goal is to obtain an organoid bank from diverse participants, there is no discussion of how the applicant will achieve this. • The project upholds 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: 7.0

Up to 7 patient advocate and nurse members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	0	*none*
6-8: Responsive	1	• Adequate DEI response
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	TRAN1-16213
Title (as written by the applicant)	Manufacture and regulatory processing of cone progenitor cells for treating central vision loss
Translational Candidate (as written by the applicant)	Cone progenitor cells (CPCs), when injected into the retina, regenerate cone photoreceptors, which are responsible for central, color, and high-acuity vision.
Area of Impact (as written by the applicant)	Inherited retinal diseases in which cones are lost (particularly cone dystrophies); acquired retinal degeneration (age-related macular degeneration)
Mechanism of Action (as written by the applicant)	CPCs are broadly (i) neuroprotective, that is they protect rods and cones in animal models prone to rod and cone degeneration. In addition, CPCs efficiently (ii) (re)generate cones in animals that are genetically susceptible to cone death. Thus, both cell replacement and cell protection are mechanisms of action.
Unmet Medical Need (as written by the applicant)	Patients with cone dystrophies have no therapeutic options and experience devastating reduction in quality of life. CPCs have potential to slow photoreceptor degeneration and to replace lost cones and lost cone function. We anticipate that CPCs will mediate a potent therapeutic effect - and reverse central vision loss - in patients who have no other options available.
Project Objective (as written by the applicant)	Pre-IND meeting scheduled
Major Proposed Activities (as written by the applicant)	• Two engineering run CPC banks manufactured (including aseptic validation and stability testing). This activity is divided into four milestones. • IND regulatory document package preparation: An INTERACT meeting ~9 months into the project, pre-IND meeting scheduled by project completion
Statement of Benefit to California (as written by the applicant)	CPC will afford patients with central vision loss a meaningful therapeutic option. CPCs will be the first therapy for central blindness due to cone dystrophy, and a critical component of treating central blindness from macular degeneration, a common disease of older Californians. The poor quality of life associated with central vision loss cannot be overstated - CPCs can address these devastating diseases.
Funds Requested	$2,380,804
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	66
Median	65
Standard Deviation	5
Highest	75
Lowest	55
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 5 **No:** 6	• Yes, targeting cone cell loss in retinitis pigmentosa, cone-rod dystrophy and cone dystrophy would address a significant unmet need. • This project aims to treat inherited retinal disease (IRD) with Cone Progenitor Cells (CPCs) isolated from fetal eye tissue and then expanded and sorted. While quite rare, IRDs present early in life and currently there is no treatment or cure. Therefore, this cell therapy has the potential to impact an unmet medical need. • The project is aimed at developing manufacturing technology with a CDMO. It is possible that this novel therapy could impact a subset of IRDs, but at the moment the applicants have little evidence of efficacy in animal models. • It is hard to know the potential for impact because of the paucity of animal data. The manufacturing plan appears feasible, but why develop and manufacture this product without more efficacy data in animal models? • Rod and cone dystrophies represent a large unmet clinical need. However, the project lacks proof-of-concept data and a nonclinical testing strategy to be able to reach pre-IND, a pre-requisite for TRAN1 funding. • The application still presents insufficient preliminary data.
GWG Votes	**Is the rationale sound?**
Yes: 3 **No:** 8	• No. There is a serious lack of pre-clinical data. This has not been addressed in this resubmission. • Technically the use of cone progenitor cells to treat cone disorders is a valuable proposition. However, the applicants have not addressed the prior reviewer requests for clearer proof-of-concept. The applicant instead indicated that advice from third parties suggested no further nonclinical data was needed and/or that studies were ongoing. Therefore, the proof-of-concept studies are not sufficient to warrant funding of a cGMP program. • The applicant needs to do the necessary pre-clinical work to demonstrate an efficacy signal. • With further animal model efficacy data there may be a case for further development.
GWG Votes	**Is the project well planned and designed?**
Yes: 2 **No:** 9	• The CMC strategy appeared to be well-considered. However, the project needs proof-of-concept: longer experiments, different animal models, histological evidence of functional integration, positive functional data (ERG and OKN), details of electrodiagnostics (e.g. test conditions under which the ERGs are performed), and evidence that the benefits are due to human cone integration and not a neuroprotective effect of the cell injections. • A panelist notes spending a large amount of money on manufacturing is inappropriate until convincing efficacy data has been produced. • Once convincing efficacy data are generated, the manufacturing activities are appropriate. • It would be fruitless to submit a pre-IND package without convincing efficacy data.
GWG Votes	**Is the project feasible?**
Yes: 3 **No:** 8	• Yes. The manufacturing will be performed by a CDMO that is well-qualified to undertake the manufacturing of this product. • The contingency plan for manufacturing is reasonable. • No. While the milestones appear reasonable, the selected CDMO may not be able to execute the manufacturing plan. • Under the circumstances, based on two rounds of review, the project is not currently feasible. • The lack of efficacy data makes the project untenable.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 6 **No:** 5	• Issues raised in the previous review of this proposal have been addressed. • There is a paucity of data on the occurrence of IRDs in non-white populations; these conditions are probably under-diagnosed. What is needed is more screening of diverse populations. • The project is based on cell manufacturing and if successful could benefit all people. Under-diagnosis is the primary issue here. • DEI was only minimally addressed. • Adequate.

DIVERSITY, EQUITY, AND INCLUSION (DEI)

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

DEI Score: 7.0

Up to 7 patient advocate and nurse members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

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