TRAN AWARDS

1/30/25

$57,495,823 GWG RECOMMENDED

$2,504,177 REMAINING

$60,000,000 AMOUNT AVAILABLE

$0 BOARD APPROVED

							Score Range		Number of GWG Votes			
APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Resubmission	Previous CIRM Funding
TRAN1-16924	A novel non-genotoxic antibody conditioning therapeutic to expand access to and safety of HSCT and CD34+ gene therapies	**$4,043,427**	**Y**	**96**	93	7	70	99	13	2	N	N
TRAN1-16935	Parkin Gene Therapy for Parkinson's Disease	**$2,450,510**	**Y**	**93**	92	3	85	95	14	0	Y*	N
TRAN1-16959	A Novel Gene Therapy to Target Glioblastoma via Custom-Engineered Adenovirus-Associated Viral Vectors	**$5,927,454**	**Y**	**93**	91	5	75	95	13	1	Y*	N
TRAN1-16998	FM-IL2 CAR T cells for Pancreatic Cancer	**$5,644,776**	**Y**	**91**	91	5	85	97	13	0	N	N
TRAN1-16919	Hematopoietic Stem Cell Gene Therapy for Alpha Thalassemia	**$5,620,230**	**Y**	**90**	91	3	90	99	15	0	N	Y
TRAN1-16965	Evaluation of an ex vivo lentiviral gene therapy for the treatment of Angelman syndrome	**$5,843,083**	**Y**	**90**	90	3	82	95	14	1	Y*	N
TRAN1-17069	A targeted antisense oligonucleotide therapeutic strategy for Timothy syndrome	**$5,596,629**	**Y**	**90**	89	2	83	90	14	1	Y*	N
TRAN1-16978	Development of an AAV Epigenetic Gene Therapy for Gain-of-Function SCN9A Disorders and Chronic Pain	**$3,982,633**	**Y**	**88**	88	2	84	92	14	1	Y*	N
TRAN1-16960	Genetic Therapy Targeting mHTT mRNA and Somatic Expansion to Treat Huntington's Disease	**$4,618,687**	**Y**	**87**	87	2	85	90	15	0	Y*	N
TRAN1-16943	Invariant natural killer T cells expressing a chimeric antigen receptor for clinical use	**$6,130,982**	**N**	**87**	86	6	70	90	13	2	N	Y
TRAN1-16956	Hypoimmunogenic iPSC-derived TCR-NK cells for oncology	**$4,100,845**	**N**	**87**	84	10	60	90	12	2	Y	N

APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Resubmission	Previous CIRM Funding
TRAN1-17000	GlyTR2 CAR T cell translation: safe pan-cancer killing via velcro-like density-dependent targeting of cancer glycans	**$4,581,144**	**Y**	**85**	86	1	85	90	14	0	Y	Y
TRAN1-16994	A gene therapy for the treatment of congenital lipodystrophy	**$4,000,000**	**Y**	**85**	85	3	75	88	13	2	N	N
TRAN1-16986	Development of an off-the-shelf iPSC derived CAR T cell therapy for the treatment of solid tumors	**$4,000,000**	**Y**	**85**	84	5	70	88	11	3	N	Y
TRAN1-16912	Next-generation, Cytokine-armored CAR-T Cell Therapy for Glioblastoma	**$5,216,915**	**N**	**85**	84	5	70	89	9	6	N	Y
TRAN1-16907	Hematopoietic Stem Cell Gene Therapy for MPSIIIB (Sanfilippo B) Syndrome	**$5,211,756**	**N**	**85**	82	4	75	88	8	7	N	N
TRAN4-17158	Purpose built cell engineering for rapid manufacturing of stem-like cell therapies	**$1,187,250**	**Y**	**85**	79	11	50	86	8	7	N	N
TRAN1-16938	iPSC-derived Thymic Epithelial Cells as Novel Cell Therapy for T Cell Reconstitution in Congenital Athymia Patients	**$6,000,039**	**N**	**84**	83	3	75	86	2	12	Y	N
TRAN1-16933	Novel CD19 CD20 Dual Targeting Allogeneic CAR-T Therapy in Multiple Sclerosis	**$3,991,879**	**N**	**83**	81	4	70	85	2	13	N	N
TRAN3-17055	Synthetic cells for immune cell engineering and immunotherapy	**$2,810,619**	**N**	**80**	79	4	70	85	1	14	N	Y
TRAN1-17022	Coalescent™ CD19-CAR NK cells Secreting an anti-NKG2D–anti-CD22 Bispecific Antibody for the treatment of relapsed or refractory B Cell Malignancies	**$4,000,000**	**N**	**80**	79	3	70	80	0	15	N	N
TRAN2-16931	Comparative Analysis of RNA Expression (CARE) to define developmental biomarkers and targets for pediatric malignancies	**$1,828,777**	**N**	**80**	75	6	65	81	0	15	N	N
TRAN4-16946	Automation to Standardize and Scale Cell Therapy Delivery	**$861,592**	**N**	**80**	72	11	50	80	0	14	N	N
TRAN1-16966	Advancing a non-viral high-fidelity KLKB1 gene editing candidate for hereditary angioedema	**$4,322,830**	**N**	**79**	77	7	60	85	2	11	N	Y
TRAN1-16950	Autologous anti-PSMA CAR-T cell controllable by focused ultrasound (FUS-PSMACAR-T cells)	**$5,492,879**	**N**	**78**	78	8	65	90	4	10	N	N

APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Resubmission	Previous CIRM Funding
TRAN4-17058	hiPSC MPS (organ-chips) based drug screening platform for age-associated degenerative diseases.	**$1,614,000**	**N**	**70**	69	7	55	82	0	15	N	N
TRAN1-17005	A humanized monoclonal antibody for the therapy of acute kidney injury and chronic kidney disease	**$4,893,012**	**N**	**60**	64	6	60	80	0	15	N	Y
TRAN1-17059	Engineering iPS Cell-based Therapy for Parkinson's Disease	**$4,501,206**	**N**	**60**	58	9	50	75	0	15	Y	Y

*Indicates application that scored 85 or above in previous cycle but was not funded due to budget limit.

Application #	TRAN1-16924
Title (as written by the applicant)	A novel non-genotoxic antibody conditioning therapeutic to expand access to and safety of HSCT and CD34+ gene therapies
Translational Candidate (as written by the applicant)	The candidate is a combination of two monoclonal antibodies targeting receptors expressed on hematopoietic stem cells (HSCs).
Area of Impact (as written by the applicant)	Replacing current chemotherapy for bone marrow transplants with a non-toxic, healthy tissue-sparing targeted antibody approach.
Mechanism of Action (as written by the applicant)	The antibody combination binds and subsequently depletes hematopoietic stem cells in the bone marrow to enable a highly specific non-genotoxic stem cell conditioning for bone marrow transplants.
Unmet Medical Need (as written by the applicant)	Bone marrow transplants (BMT) have great curative potential but currently require chemotherapy/irradiation-based preparation or conditioning to eradicate diseased stem cells and create room for transplanted cells. Standard conditioning has acute and long term toxicities. Our new approach to conditioning replaces chemotherapy with a safer, non-genotoxic antibody-based regimen that aims to reduce conditioning-related morbidity and mortality and thus greatly expand patient access to curative BMTs.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• In vivo PK/PD studies to determine dose and dosing regimen for therapeutic antibody combination • Initiate cell line development for the two monoclonal antibodies to generate a toxicology lot for each antibody candidate • In vitro pharmacology and toxicity studies • Establish and implement ADA assays and validate PK assays for both therapeutic candidates • Pre-IND package submission and successful pre-IND meeting
Statement of Benefit to California (as written by the applicant)	HSCT can be a curative treatment for non-malignant genetic disorders such as sickle cell disease. Conditioning is required to prepare your body to receive incoming stem cells and is currently achieved through toxic chemotherapy and/or irradiation. We are developing a novel antibody-based conditioning regimen that is highly specific and non-genotoxic. We aim to expand patient access to and increase safety of HSCT to the thousands of people in California who are seeking such life-changing cures.
Funds Requested	$4,043,427
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: 96

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	96
Standard Deviation	7
Highest	99
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	2

Key Questions and Comments

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/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 potential to reduce the morbidity and mortality of HSCT would address an important unmet medical need. • The product would likely improve the success of hematopoetic stem cell transplantation. • The proposed product offers a value proposition for both patients and health care providers. • This is a clever and innovative approach to conditioning that can have a high impact across all applications of HSPC based therapies, including transplants. • The project addresses a highly significant, relevant unmet medical need.
GWG Votes	**Is the rationale sound?**
Yes: 13 **No:** 0	• The preliminary data support the rationale for proposed target indication. • The rationale is sound and supported by the bulk of the scientific data in the application. • The applicant provides a very strong application from a strong team. The work is logistically feasible and stage appropriate for TRAN1.
GWG Votes	**Is the project well planned and designed?**
Yes: 13 **No:** 0	• Strengths include: the understanding of regulatory expectations for co-developing two investigational agents, the selected animal species for the proposed POC study, and stage-appropriate pre-IND planning. • The planning for this project is excellent. • With very well planned experimental designs, this strong application is likely to achieve its milestones and overall goals.
GWG Votes	**Is the project feasible?**
Yes: 13 **No:** 0	• No concerns about project feasibility. • The planned studies are reasonable and will enable achieving a pre-IND meeting within the proposed timeline. • This strong team, aware of both scientific and regulatory landscape, is highly likely to complete the proposed work and produce important results.

GWG Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
Yes: 13 **No:** 0	• A specific, well-designed DEI plan is provided. • OK. • The DEI plan is in line with the phase of the project. • The project upholds all principles of DEI.

Application #	TRAN1-16935
Title (as written by the applicant)	Parkin Gene Therapy for Parkinson's Disease
Translational Candidate (as written by the applicant)	An AAV-based gene therapy to deliver the Parkin gene to Parkinson's Disease Patients with biallelic mutations in the Parkin gene.
Area of Impact (as written by the applicant)	The proposed gene therapy will restore health to the cells that are dying in Parkinson's Disease (PD), restoring normal movement.
Mechanism of Action (as written by the applicant)	Parkin gene therapy will restore health to the diseased cells in Parkinson's Disease (PD). By restoring normal function, the therapy will regenerate homeostasis of dysfunctional brain circuits involved in movement. It will be the first genetic cure for PD, establishing a new treatment paradigm for advanced medicines in neurodegenerative diseases. The mechanism of action to repair mitochondria allows for impact in a variety of mitochondrial dysfunction disorders beyond PD.
Unmet Medical Need (as written by the applicant)	There are no disease-modifying therapies for PD. The proposed gene therapy targets the most common genetic cause of PD by restoring Parkin, a neuroprotective factor known to reinstate health to diseased cells. It will be the first curative therapy for the movement disorder associated with PD, dramatically improving quality of life for PD patients in California and the world. Because Parkin restores mitochondrial health, this therapeutic approach can address additional indications with critical unmet medical need.
Project Objective (as written by the applicant)	Conduct 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 • Clinical Planning, Protocols and Synopsis for Phase 1 • DEI Outreach Activities • Pre-IND meeting with the FDA
Statement of Benefit to California (as written by the applicant)	Parkinson's Disease is creating an increasing health burden to California at alarming rates. Our product will provide a novel, disease-modifying therapy to dramatically reduce economic and social burden for California, including patients and healthcare providers, through our drug's regenerative activity for genetic and environmental etiologies of PD. We will remove research bottlenecks by defining biomarkers and assays to promote additional therapeutic development for this validated target.
Funds Requested	$2,450,510
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	3
Highest	95
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	• The proposed AAV-based drug product for the treatment of Parkinson's Disease (PD) could provide a disease-modifying option that would surpass the current standards of care. • The proposed product would surpass the current standards of care and therefore be quite impactful for patients and health care providers (HCPs). • This is an excellent proposal and has the necessary significance and potential to make a significant impact. • If successful, the development of the proposed AAV product would significantly improve patient care. • Parkinson's is an important disease.
GWG Votes	**Is the rationale sound?**
Yes: 12 **No:** 0	• This resubmission is a significant improvement on the prior application. • The science is strong, and the applicant has generated substantive pre-clinical data supporting the overall rationale. • Yes, the project is based on sound rationale. The CMC plans are sufficient for an IND and Phase 1 study. • The rationale is supported by the body of available data.
GWG Votes	**Is the project well planned and designed?**
Yes: 12 **No:** 0	• There is significant improvement on the last application. Timelines will be tight. • This application is well planned and has improved since the last submission. • The INTERACT meeting was held and activities have been agreed upon. • This is well-constructed program.

GWG Votes	Is the project feasible?
Yes: 12 **No:** 0	• Timelines will be tight. • Yes, this application has a high probability of success. • The project seems feasible, notably from a CMC perspective. • The proposed team is appropriately qualified. • The team has access to all the necessary resources to conduct the proposed activities. • The team has a viable contingency plan to manage risks and delay.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12 **No:** 0	• Improved DEI application. • Yes, the applicant has done a great job addressing prior critiques of their DEI section.

Application #	TRAN1-16959
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 AAV2-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 has few treatment options.
Mechanism of Action (as written by the applicant)	The novel gene therapy involves the introduction of a targeting gene cassette T6 that will be delivered directly into GBM cancer stem cells (GSC) using a highly potent vector rAAV2-Mut9 derived from the clinically proven vector AAV2. T6 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 T6 for a planned Pilot study. • Optimize a brain infusion method to deliver T6 using a CED and confirm the optimal protocol for T6 in PDX to prepare for a pre-IND meeting. • Conduct pharmacodynamics study with T6 as compared to T1 control. • Conduct a pilot safety study to determine the MTD of T6 in non-tumor bearing mice and in regular and humanized PDX to prepare for a pre-IND meeting. • Confirm efficacy of T6 vs T1 in regular and humanized PDX using the MTD to prepare for a pre-IND meeting. • Prepare pre-IND package and meet with the FDA.
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	$5,927,454
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	91
Median	93
Standard Deviation	5
Highest	95
Lowest	75
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: 12 **No:** 0	• Glioblastoma continues to be a cancer that is difficult to treat. The proposal takes a novel approach and thus there is potential for benefit compared to previous and current approaches. A multi-pathway approach appears to be effective in controlling tumor growth and is rooted in targeting a fundamental reason the tumor may escape other treatment options. • 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.
GWG Votes	**Is the rationale sound?**
Yes: 12 **No:** 0	• The preliminary data are improved from the prior submission. • Basic research efforts in this project are extensive and expansive. It appears the group is taking a comprehensive view in how to identify and target key points in tumor cell survival and escape. The clinical rationale for development is strong. Plans for application have not been well described but this can be worked out as the program matures. The team has worked through the MOA and has demonstrated the hypothesis is accurate for the biologic effect. • By focusing on master regulators (MR) that appear to govern shared GBM characteristics, there is the possibility of circumventing GBM heterogeneity. Using a novel computational platform, 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. • The goal is to pioneer a first-of-its-kind, heterogeneity-agnostic gene therapy that targets GBM. They have engineered highly efficient vectors derived from adeno-associated virus 2 (rAAV2) to deliver a shRNA cassette designed to deplete the GBM state MRs in GSCs. • The lead variant displays up to 40-fold higher efficiency than wild-type AAV2 and other tested variants in transducing GBM cells. • They introduced six shRNA cassettes into rAAV2 to deplete key GBM state MRs, and are focusing on the one that shows the most potent efficacy. This vector achieves cure rates of 70-90% in their model. • To overcome GBM's profound heterogeneity, they identified a common GBM state that transcends the molecular heterogeneity of GBM tumors. They demonstrated that by targeting key master regulators (MR) controlling the common GBM state, they eliminated the GBM fate and circumvented the heterogeneity in a broad panel of patient-derived GSCs. • They generated highly efficient and GBM-selective vectors derived from a complex rAAV2 library. The lead candidate vector exhibits 40-fold higher efficiency over parental AAV2 for transducing diverse populations of GBM cells including both GSCs and non-GSCs. • They engineered a shRNA cassette that efficiently depletes critical MRs of the GBM state. The lead candidate commands the most consistent and potent efficacy in disease models, with maximal cure rates of 70-90% and is selected for clinical development. • Using a micropump, they demonstrated successful delivery of AAV2 into a growing GBM tumor with 10-fold higher efficiency compared to a single intratumor injection of the same viral dose. • Even with the suboptimal single intratumor injection of the lead candidate, however, they showed that the transgene efficiently covered the entire tumor and spread to the invasive front and peritumor region where it infected infiltrating GSCs and induced apoptosis. • They have identified 2 MR hubs that provide overlapping control of the 3 regulatory pathways they identified. • They also did gain-of-function experiments. They reconstructed the 2 MR clusters separately in human astrocytes and found that a subset of astrocytes formed spheres in stem cell media. When implanted in the brains of NSG mice, these astrocytes formed lethal infiltrative brain tumors in mice by 6-8 months compared to normal life spans in mice injected with control astrocytes. That transformation occurs without the introduction of a single driver mutation is strong evidence of a GBM state. • The safety analysis has been strengthened with the addition of studies on neural stem cells, oligodendrocyte precursor cells and other cell populations to determine if disruption of the master regulator network is safe for normal precursor cells, and with preliminary data showing greatly increased expression of this network in GBM cells.
GWG Votes	**Is the project well planned and designed?**
Yes: 12 **No:** 0	• Manufacturing, efficacy and clinical plans seem appropriate. The non-clinical safety plan is not well described. • In the preclinical phase of pharmacodynamics and pharmacokinetics, they will use both sex-specific and age-specific disease models in NSG mice to recapitulate the diversity of GBM patients. They will also use donor materials from diverse epigenetic subgroups, from both male and female patients, and whenever detailed demographic information is available, also from different racial and ethnic backgrounds. • For pilot safety studies, they will use mice from 4 independent inbred and 3 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 the genetically and racially diverse patient populations of GBM. • The manufacturing processes involve the GMP-compatible plan of graduating culture vessel size from the standard small shaker flask format to small stirred tank bioreactors (BR) to large BRs using cells specifically optimized for suspension culture and large-scale efficient protein production. This is an industry standard approach to produce rAAV for clinical applications. • *[Key Person's name redacted]* was a founding director of the vector core laboratory of the gene therapy center at *[institution name redacted]* in the 1990s. Since then, his lab has developed multiple AAV vectors, plasmid DNA helpers, novel production platforms, and purification protocols that have now become industry standards, as described in the Process Development. • Methods and assays pioneered by *[same Key Person]'s* vector core lab were subsequently incorporated into large-scale GLP/GMP production protocols in the highly successful *[same institution]* 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.
GWG Votes	**Is the project feasible?**
Yes: 12 **No:** 0	• Manufacturing and efficacy studies 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 of absolute failure in efficacy or tolerability). The nonclinical safety plan is high level and difficult to review at this time. • *[Same Key Person]'s* lab has developed and adapted multiple strategies to handle potential batch-to-batch variability to ensure product consistency and stability through robust manufacturing and Quality Control processes. This lab is a pioneer in vector development and analysis.
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 re-submission builds on what was already a strong application component. • The applicant 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 applicant cancer center's Office of Community Outreach and Engagement (COE) and the applicant institutional translational science institute also contribute to DEI efforts. These offices inform diverse communities about cutting-edge treatments, including gene and stem cell therapies, and work with community advisory boards to bridge the gap between scientists and communities. • A key partnership in the applicant's DEI strategy is with a CIRM Alpha Clinic team that is renowned for commitment to diversity and inclusion in patient recruitment for clinical trials. The Alpha Clinic team will help design and execute a recruitment strategy for the diverse population affected by GBM. The associate director of the Alpha Clinic is a collaborator on this grant, and his expertise in clinical translation is coupled with a deep commitment to DEI.

Application #	TRAN1-16998
Title (as written by the applicant)	FM-IL2 CAR T cells for Pancreatic Cancer
Translational Candidate (as written by the applicant)	An autologous CAR T cell therapy for pancreatic cancer that uses "AND" gate logic for enhanced precision and inducible IL-2 for enhanced potency.
Area of Impact (as written by the applicant)	Pancreatic cancer is one of the most dangerous malignancies with few effective treatments and so far, no approved immune based therapies.
Mechanism of Action (as written by the applicant)	Pancreatic cancer presents an elusive target for the immune system. Here we will reprogram patient T Cells to recognize and then trigger their cell-killing activity using a more precise two-factor (AND gate) recognition program unique to the tumor and not healthy tissue. These T cells will also be programmed to locally produce powerful immune-stimulating drugs directly within the cancer dramatically improving the ability of these T cells to self-amplify and clear challenging tumors.
Unmet Medical Need (as written by the applicant)	Pancreatic cancer is the third leading cause of cancer death in the United States, with a five-year survival rate after diagnosis of only 9%. This is one of the lowest for any type of malignancy. Unfortunately, many of the new tools to treat cancer such as targeted therapies or immunotherapies have had minimal impact on the treatment of this disease. Clearly, we need completely new, more sophisticated, and powerful tools to attack pancreatic cancer.
Project Objective (as written by the applicant)	Pre-IND
Major Proposed Activities (as written by the applicant)	• Process Development: Establish standard operating procedures for clinical manufacturing of FM-IL2 T cells. • Product Verification: Perform in vitro and in vivo assays to confirm the activity of FM-IL2 T cells manufactured using clinical manufacturing SOPs. • Assay Development: Develop analytical assays for CAR induction from manufactured product for product release criteria and therapy dosing.
Statement of Benefit to California (as written by the applicant)	California will benefit greatly from the development of a therapy that can meaningfully impact the standard of care for pancreatic cancer. Currently every year there are around 4,000 new cases of pancreatic cancer diagnosed in California, 75% of whom are already at a late stage. Engineered T cell therapies offer the potential of a single curative treatment that will not only greatly reduce disease morbidity and mortality in the state, but also potentially reduce the total cost of care.
Funds Requested	$5,644,776
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: 91

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	91
Standard Deviation	5
Highest	97
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	• The proposed product is likely to impact pancreatic cancer. • This is a genetically engineered cell therapy to target stromal cells and induce expression of CAR and cytokine to exert tumor-specific cytotoxicity and improve persistence. • The ability to deliver chimeric antigen receptor (CAR T) cells with improved specificity and persistence is critical for an effective therapy. • This rational innovation improves upon prior iterations of CAR T cell therapies that may offer impact for patients. • Yes, there is high unmet need for pancreatic cancer. Pancreatic cancer has been resistant to treatment by CAR T and other immunooncology therapeutics. This is an interesting therapeutic strategy that if effective would have a significant impact.
GWG Votes	**Is the rationale sound?**
Yes: 11 **No:** 0	• The applicant has considered the limitations in evaluating CAR T cells in immune-deficient preclinical xenograft models and designed a therapeutic analog in competent preclinical models to answer additional questions supporting safety and efficacy. • The proposed product has been designed to specifically address the current challenges of CAR T cell therapies. • Yes, several limitations of CAR T cells for pancreatic cancer exist. Target antigen, dense stroma, lack of T-cell supporting nutrients. This proposal aims to integrate all of these to develop an improved therapy. • Yes, the preliminary data provided is convincing and demonstrates that the FM-IL2 CAR T product improves the function of this therapy while decreasing off-target toxicity. • Yes, the data supports the development of the product. • The outlined experimental data is supportive of this approach.

GWG Votes	Is the project well planned and designed?
Yes: 11 **No:** 0	• Yes, the next steps for product development are discussed. This proposal, if successful, will ready the product for IND submission. • The goal is to develop a data package to enable an INTERACT meeting followed by a pre-IND meeting. The described activities seem appropriate for these goals. • The project appears feasible, particularly from a CMC perspective. The manufacturing plan seems straightforward with the biggest tasks being the development of appropriate characterization and release assays as well as determining and controlling dose models. • Preclinical data is supportive. Clinical trial outline is sufficient for a pre-IND. Clinical Trial protocol, investigator brochure, manuals and Informed Consent Form (ICF) would not be needed at this stage.
GWG Votes	**Is the project feasible?**
Yes: 11 **No:** 0	• Yes, and risk mitigation strategies are clearly defined.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 11 **No:** 0	• The applicant's DEI plan is specific.

Application #	TRAN1-16919
Title (as written by the applicant)	Hematopoietic Stem Cell Gene Therapy for Alpha Thalassemia
Translational Candidate (as written by the applicant)	Autologous hematopoietic stem cells (HSC) from patients with alpha thalassemia major modified with a vector expressing a therapeutic alpha-globin gene
Area of Impact (as written by the applicant)	This candidate targets the condition of alpha thalassemia for which there are no currently available cures that are both safe and effective
Mechanism of Action (as written by the applicant)	The proposed candidate is a stem cell product manufactured from each patient's own hematopoietic (blood forming) stem cells. Hematopoietic stem cells are collected from the patient, modified using a virus to add a therapeutic alpha-globin gene, and transplanted back into the patient. Upon engraftment of the stem cells in the bone marrow, the gene-corrected cells will be a durable, life-long source of RBCs containing a functional alpha-globin protein, effectively curing the disease.
Unmet Medical Need (as written by the applicant)	Patients with alpha thalassemia major are dependent on life-long RBC transfusions and suffer severe organ damage and early mortality from iron overload. Transplant of allogeneic hematopoietic stem cells (HSC) can be curative, but has life-threatening risks of graft versus host disease (GVHD) and severe infection. With autologous HSC gene therapy (GT), the patient is a perfectly-matched donor, has no risks of GVHD,, and does not require immune suppression, . GT could provide a safer treatment.
Project Objective (as written by the applicant)	Hold a well-prepared preIND meeting with FDA
Major Proposed Activities (as written by the applicant)	• Manufacture clinical-grade virus containing the therapeutic gene • Perform laboratory testing to ensure that virus meets quality and safety standards • Demonstrate at-scale manufacturing of the stem cell product • Perform quality and safety testing • Perform stability studies • Perform a toxicology study of the human stem cell product in an immune deficient mouse model to confirm product safety • Perform FDA-required genotoxicity safety testing of the clinical-grade virus using a specialized assay • Prepare a draft clinical protocol • Prepare study reports • Hold a PreIND meeting with FDA
Statement of Benefit to California (as written by the applicant)	Safe, definitive therapies for Alpha thalassemia major (ATM) represent a growing unmet medical need. Allogeneic stem cell transplant is frequently complicated by life-threatening graft-versus-host disease and severe infections due to immune suppression. Successful demonstration that stem cell gene therapy can safely and effectively cure ATM will shift the paradigm by which patients will be treated, led by California's position as a leader in the field of gene therapy. This will result in improved patient care in the state and around the world.
Funds Requested	$5,620,230
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***
Process Vote	*All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG."* *Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."*

Scoring Data

Final Score: 90

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

Mean	91
Median	90
Standard Deviation	3
Highest	99
Lowest	90
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	15
(1-84): Not recommended for funding	0

Key Questions and Comments

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 13 **No:** 0	• This project targets alpha thalassemia. This is a rare condition which can be mitigated by transfusions but does not currently have a curative therapy. If successful this product could be curative for the patient population. • Yes, while alpha thalassemia major has the ability to be treated with repeated long term transfusions patients have high risks for complications from iron overload, ineffective erythropoiesis, and hemolysis. The proposed product is a gene modified HSC treatment that would address the underlying lack of alpha globin gene expression. • This product could provide a curative treatment for patients with alpha thalassemia but it will require that patients be treated at specialized centers, requiring patients to travel, parents/patients to miss work and identify childcare for siblings/children. The cost of the product is likely to be high which may result in reimbursement issues with insurance companies/public healthcare systems.
GWG Votes	**Is the rationale sound?**
Yes: 13 **No:** 0	• Yes, this product has been developed based on/and is similar to a commercially available product used to treat beta thalassemia. • Yes, treatment of alpha thalassemia major by autologous gene modified HSC transplant with constructs appropriately designed for replacement gene expression is a sound scientific strategy. It has been used successfully in beta thalassemia.
GWG Votes	**Is the project well planned and designed?**
Yes: 12 **No:** 1	• Yes, the project includes all activities necessary to meet the program objective of a pre-IND meeting however it is not obvious that a pre-IND meeting is required here. From other experiences with similar products and the well-defined expected outcomes of the activities described here it would seem that an IND could be filed at the end of this project. • The bulk of the CMC work and toxicology studies proposed are usually done post pre-IND and are IND supporting work. While the clinical plan clearly would benefit from a pre-IND meeting the bulk of the activities may be more appropriate for a CLIN-1 grant. In the regulatory correspondence section the FDA denied an additional INTERACT request stating that the program was sufficiently advanced for a pre-IND.

	• Proposed GLP toxicity study is out of scope for TRAN grant; as such recommend deleting.
GWG Votes	**Is the project feasible?**
Yes: 13 **No:** 0	• Yes, this is an experienced team with a proven track record in the field. The funding is de-risked. This is an extremely feasible project. • From a CMC perspective the project is well designed and planned and appears to be highly achievable.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13 **No:** 0	• The disease is primarily seen in individuals of asian ancestry so there are some diversity issues related to this specific product. However, if successful the technology being studied here can be modified for use in other diseases and patient populations. There are some risks of limited availability of this product in underinsured patients. • Yes, in as much as possible for a rare disease. This disease predominantly affects those of asian ancestry, particularly of southeast asian and southern chinese descent. This team has a good approach to DEI and experience in patient informed clinical trial design.

Application #	TRAN1-16965
Title (as written by the applicant)	Evaluation of an ex vivo lentiviral gene therapy for the treatment of Angelman syndrome
Translational Candidate (as written by the applicant)	Lentiviral transduced CD34+ cells
Area of Impact (as written by the applicant)	Area of impact is Angelman Syndrome. Lentiviral vector manufacturing and CD34+ cell drug product manufacturing are identified bottlenecks.
Mechanism of Action (as written by the applicant)	Lentiviral-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 patients) to cross correct the surrounding neurons.
Unmet Medical Need (as written by the applicant)	Currently there is no cure for Angelman Syndrome
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 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 a lentiviral vector has proven to be an efficient means to replace a deficient enzyme in other CNS disorders via cross correction. This new therapy being proposed here will provide a viable treatment for children born with Angelman Syndrome in California and beyond the state borders.
Funds Requested	$5,843,083
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***
Process Vote	*All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG."* *Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."*

Scoring Data

Final Score: 90

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

Mean	90
Median	90
Standard Deviation	3
Highest	95
Lowest	82
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	1

Key Questions and Comments

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 13 **No:** 0	• This is a resubmission of a project that is focused on advancing a hematopoietic stem cell gene therapy (HSCGT) for Angelman syndrome (AS), a disease that is associated with a normal life span but leads to epileptic seizures, ataxia, absent speech, and dysmorphic facial features to various degrees. All patients have, however, severe mental retardation and speech disorders. Angelman syndrome is estimated to be between 1 in 10,000 and 1 in 40,000 births and its management puts severe burden not only on patients but also caretakers. • This is a resubmission. Applicants address all reviewers' questions and significantly improved the proposal. • There is no cure or good therapeutic options for Angelman syndrome. Therefore, it represents an unmet medical need. • The proposed product has the potential to provide a cure or diminish disease progression. • There is no cure or approaches that would modifying/delay pathology The disease is defined by mutations in the ubiquitin protein ligase E3A (Ube3A) gene, which is exclusively expressed in brain from the maternal allele and shows tissue specific imprinting. The product could be curative or at least delay the pathology. • Treatment options for Angelman syndrome continues to be limited in scope and provide modest improvement. If successful, this could represent a means to correct the underlying cause and minimize the need for supportive care.
GWG Votes	**Is the rationale sound?**
Yes: 13 **No:** 0	• The rationale is sound. The disease is caused by a mutation in a single gene (Ube3A). The lentiviral vector with a normal Ube3A aimed to normalize the function. • Preliminary data presented in the proposal support the rationale. • The rationale is sound and has been developed for other diseases. The hematopoietic stem and progenitor cells (HSPC) transduction will occur *ex vivo* with a lentiviral vector (LV) carrying a Ube3A sequence that encodes for a modified human protein under the control of a physiologic promoter with the idea to restore function. • HSCGT therapies have gained traction and have approval for the FDA for a number of other diseases. The use of LV is a common strategy. • A robust phenotypic rescue has already been seen in a similar (published) study where the authors used a novel immunodeficient Ube3A-/+ mouse model combined with engineered human CD34+ cells transplantation. • The initial study was based on a promoter that has not been accepted by the FDA. The applicants thus needed to switch to a different promoter that has not been associated with malignancies. The proposal is basically a repeat of previous studies as there is no right of reference to the prior Pre-IND application. • The proposal has a sound scientific rationale, although certain aspects, such as sufficient protein uptake throughout the CNS, must be confirmed. Under and over expression will need to be confirmed (positive or negative) to better understand the true potential. The clinical plan has not yet been established. It is noted the procedure is intensive and this will need to be addressed for patients (or their parents/guardians) to consider this a reasonable treatment.
GWG Votes	**Is the project well planned and designed?**

Yes: 13 **No:** 0	• The activities in the project are guided by feedback from FDA (regulatory correspondence from 2020). The project is well planned. • It is a high quality program. • The proposed promoter used for this study acknowledges previous issues with respect to malignancies. The applicants have taken appropriate steps to circumvent this issue. • The applicant considered feedback from their pre-IND meeting and adjusted milestones accordingly. For example, they now incorporated electroencephalography (EEG) analysis as suggested in the pre-IND document. • All activities and places are described; there is a logical progression of work. The objective is likely to be met. • The project plan appears to contain the required and expected activities for development of the product. At a high level the manufacturing plan appears to be sufficient. No details provided for the clinical plan in the application; the FDA response letter has responses and thus a clinical plan must exist.
GWG Votes	**Is the project feasible?**
Yes: 13 **No:** 0	• The project looks feasible. The team is well-qualified to perform the work. • The early engagement of the Contract Development and Manufacturing Organization (CDMO) at an early stage is a strength and will avoid issues with tech transfer at a later stage and comparability studies that have been shown to substantially delay commercialization. • The project is highly feasible. The applicants have conducted the very same study before with a different promoter and should be able to conduct the outlined experiments. • Timelines appear to be reasonable to achieve the projected studies. The budget may be strained, for example, one quote is from 2020 and costs have increased substantially in last 4 years.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13 **No:** 0	• The applicant addresses the potential costs of the treatment and offers that a patient advocacy group is working with global regulators and payers to help facilitate availability. No further details as to the affordability of the therapy for under served communities are provided. • AS is a primarily *de novo* condition and is likely equally distributed across races and ethnicities. However, the majority of research does not reflect diverse populations and under-served communities are not well represented. The applicant works closely with a patient advocacy group whose global registry is designed to understand the racial and ethnic distribution of AS. The advocacy group has also supported efforts to expand access to newborn screening and conducted outreach events. • The applicant is actively contributing to efforts focused on practices that will allow decentralization of trials, thus including patients of diverse backgrounds. They will provide information as to the diversity of CD34+ donor cells, will perform analysis of registry data to help identify patients in diverse socioeconomic communities, and will optimize their site selection, recruitment plan, and study protocol to minimize trial burden.

Application #	TRAN1-17069
Title (as written by the applicant)	A targeted antisense oligonucleotide therapeutic strategy 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)	Individuals with Timothy syndrome (TS) have very high rates of developmental delay, intellectual disability, autism spectrum disorder, epilepsy, and other neurologic and psychiatric disorders. We have no specific treatments to offer individuals with Timothy syndrome and no way to alter the abnormal brain development our findings suggest are taking place.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Produce lead TS1 ASO in sufficient quantity for this proposal. • Establish safety, toxicology and pharmacokinetics in rodent non-GLP studies using non-GMP ASO. • Measure pharmacokinetics and toxicology in non-human primate non-GLP studies using GMP ASO. • Measure pharmacokinetics, toxicology in mouse as GLP study using GMP ASO. • Define stability of finalized GMP TS1 ASO. • Plan, initiate, and complete pre-IND conversation with FDA.
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	$5,596,629
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	83
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	1

Key Questions and Comments

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 11 **No:** 2	• Timothy Syndrome is an ultra rare genetic disorder. This project could have significant impact for those patients. Development of an ASO could also pave the way for other targeted therapies. It is unclear whether development of this product could benefit other neurodegenerative conditions. • The disease is life-threatening and multi-symptomatic including a high risks of seizures, developmental delay/intellectual disability, and autism spectrum disorder. There is no cure for the disease and limited commercial interest in developing a therapeutic approach • While advances in clinical care have improved and patients live longer, the neurological decline limits quality of life and poses a high demand on care takers. • While the benefit of any therapy for rare diseases will be limited for the general population this therapy is based on a new model of human organoids combined with a unique transplantation approach as no animal model is available. This approach is novel approach could be adapted for many other diseases where suitable animal models are lacking and is a potential 'game changer' with extremely high impact. • The therapeutic intervention would be targeted to very young children to prevent disease rather than being tested in adults with severe disease. This is an important deviation from other FDA approaches and needs to be done. The potential impact is high. • This is an ultra-rare disease with no animal model. • This particular product is unlikely to advance the field, although has the potential to improve standard of care in TS patients. • The proposed product may impact patients suffering from Timothy Syndrome.
GWG Votes	**Is the rationale sound?**
Yes: 13 **No:** 0	• The underlying biology provides the rationale for this application and has been published in Nature in Spring 2024. Briefly, TS1 is caused by a heterozygous pathogenic variant in an alternately spliced and developmentally regulated exon of the gene CACNA1C. The idea is that switching CACNA1C splicing can reduce expression of the TS1 variant and restore function. The applicant developed an ASO to achieve this and tested its efficiency in an organoid model. • The cause of Timothy syndrome has been identified and this ASO has been developed to correct the error and restore function. The rationale is clear. • The limitation of the organoid/transplant model is the risk of potential side effects for heart function, which cannot be assessed. Mitigation is not clear. • The rationale is supported by excellent published and preliminary data. • Yes, the proposed project is sound.

	• The rationale is sound.
GWG Votes	**Is the project well planned and designed?**
Yes: 13 **No:** 0	• The non-clinical work is well described and once conducted should lead to successful submission of a pre-IND package. • All experiments are described and are sufficient. Performance sites are identified and milestones are described. • Considering the robustness of the data and the relative novelty of the efficacy models testing (i.e., organoid and transplantation approach) a pre-IND meeting at an earlier time point should be considered. It is not clear why the applicants do not seek at least some feedback advice from the FDA at this stage. • Along these lines, potential side effects to the heart caused by intrathecal injection might be a real hurdle for FDA approval. The discussion to remedy such a potential issue is minimal. • The organoid model is novel.
GWG Votes	**Is the project feasible?**
Yes: 13 **No:** 0	• The work described in this application which will lead to a pre-IND meeting is well described in the project and is feasible. • The group has shown considerable work in identifying individuals with Timothy syndrome and establishing communication with them which should allow them to enroll such subjects in a clinical trial if and when it is available. This is no easy task in an ultra-rare disorder and the investigators should be applauded for their efforts. • Patient recruitment is advancing. For example, ~40 new families with CACNA1C-related disorders have been engaged in the last year and the group has intensified outreach to other major US pediatric centers to identify additional individuals with Timothy syndrome. • Yes, the project is feasible with the proposed timeline. • The proposed team appropriately qualified and staffed. • The team have access to all the necessary resources to conduct the proposed activities. • The team has a viable contingency plan. • All technical aspects of the project are feasible. • Yes, the project is feasible.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13 **No:** 0	• There are no DEI issues with this application. As described under feasibility (above), the team has done an excellent job of reaching out to families of individuals with Timothy syndrome regardless of race/ethnicity or gender. • There are no known sex biases, but both male and female animals will be used in the efficacy experiments. • To overcome barriers for under-served communities to benefit from this approach, recruitment of individuals will occur via international outreach and engagement of all pediatric hospitals in California as well as tertiary medical centers. Applicants will engage medical interpreter services to reach non-English speaking groups in California. • As an ultra-rare disease TS is impacted by institutionalized inequity such as access to health insurance, specialist medical care, costly genetic testing and by a reluctant to provide funding or develop therapeutic approaches - the applicants try to make an impact on these inequalities. Two project leads are members of the scientific advisory board (unpaid) for the Timothy Syndrome Foundation and the Timothy Syndrome Alliance and directly engaged with patients and parents.

Application #	TRAN1-16978
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, at the DNA level, to treat chronic pain.
Unmet Medical Need (as written by the applicant)	There are currently no FDA approved drugs for 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
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	$3,982,633
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***
Process Vote	*All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG."* *Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."*

Scoring Data

Final Score: 88

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

Mean	88
Median	88
Standard Deviation	2
Highest	92
Lowest	84
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	1

Key Questions and Comments

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 12 **No:** 0	• This novel approach has the potential to impact the unmet need of chronic pain. • The platform could be expanded to chronic pain without relying on opioids. • Yes, the product could greatly improve patient care. • The applicant is developing a new drug modality with the potential to meet an unmet need for rare disease. • There is a competitor product; however, this product is anticipated to be more efficacious. • This application would meet an unmet need in patients with Primary Erythromelalgia. However, it is unclear that it could benefit patients with chronic pain more generally.
GWG Votes	**Is the rationale sound?**
Yes: 12 **No:** 0	• Epigenetic silencing of the gene that encodes for the sodium channel NAV1.7 will reduce pain. • There is precedence for AAV-based gene therapies and sound proof of concept for this indication. • Proof of concept work is strong and included new, additional data in appropriate animal models.
GWG Votes	**Is the project well planned and designed?**
Yes: 12 **No:** 0	• RIsks are well considered. The chemistry, manufacturing and controls (CMC) is substantially de-risked. • Based on the FDA response to their request for an INTERACT meeting, the team is well-poised for a pre-IND meeting. • Regulatory agency interactions provide a clear path and rationale for the next studies.
GWG Votes	**Is the project feasible?**
Yes: 12 **No:** 0	• This is good team with a strong track record. • The stated timelines seem feasible. • From a CMC perspective, the proposed timeline and milestones should be achieved.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12 **No:** 0	• Erythromelalgia is more common in women than men. The investigators state that treatment disparities for pain occur when comparing non-hispanic whites as compared to black patients and that they will strive for representation across diverse demographic groups. • DEI is well considered for patient recruitment and eventual implementation of the trials.

Application #	TRAN1-16960
Title (as written by the applicant)	Genetic Therapy Targeting mHTT mRNA and Somatic Expansion to Treat Huntington's Disease
Area of Impact (as written by the applicant)	**Area of Impact** (as written by the applicant)
Mechanism of Action (as written by the applicant)	Our genetic therapy manipulates a protein coding mRNA in brain cells by precisely binding the U1 SnRNA and a 5' donor nucleic acid sequence of the HTT and PMS1 mRNAs. This induces a modification of the mRNAs that results in destruction of the mutant huntingtin and PMS1 mRNA which have been demonstrated to cause 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)	HD has a high unmet medical need. It is a devastating neurodegenerative disorder characterized by motor dysfunction, cognitive decline, and psychiatric symptoms. Some medications alleviate symptoms, but treatments that modify the course of the disease are lacking and fail to halt the progressive nature of HD. Our proposal advances a drug that treats two disease mechansims that drive brain neurodegeneration, mHTT and CAG somatic expansion.
Project Objective (as written by the applicant)	Pre-IND Meeting and readiness
Major Proposed Activities (as written by the applicant)	• Demonstrate that the therapeutic candidate is potent in the target neuronal cell type that is affected in Huntingtons disease • Complete the toxicology profile for the therapeutic 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 applicant, a California biotech, aims to advance a therapeutic candidate for Huntington's disease (HD), potentially providing a groundbreaking, transformative 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	$4,618,687
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***
Process Vote	*All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG."* *Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."*

Scoring Data

Final Score: 87

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

Mean	87
Median	87
Standard Deviation	2
Highest	90

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

Key Questions and Comments

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 13 **No:** 0	• Huntington's disease presents a significant burden. • Yes, this project has a high potential for impact. • The proposal addresses a significant unmet medical need in Huntington's disease (HD), as current treatments focus primarily on symptom management rather than disease modification. • While the research landscape for HD is active, with numerous ongoing trials, this therapeutic candidate stands out as a small molecule therapy targeting RNA splicing. For some reason, the proposal just felt different from the cell or gene therapy that CIRM usually funds. Obviously, the application cleared the eligibility screening assessment, but this candidate invovles a very different development and CMC pathway than what usually is awarded CIRM funding.
GWG Votes	**Is the rationale sound?**
Yes: 13 **No:** 0	• The applicant presents good preliminary data. • Data from human preclinical models, including iPSCs and iPSC-derived neurons, support the candidate's rationale and its translational potential. • The applicant plans to generate data using organoid systems to assess the candidate's efficacy early on, but the proposal lacks a clear mechanism and timeline for data sharing. This raises questions about its integration into the project plan. • The rationale is sound, but the overall product profile for a small molecule drug product is atypical for a CIRM application.
GWG Votes	**Is the project well planned and designed?**
Yes: 13 **No:** 0	• Yes, this project is well planned and designed. • The candidate shows activity in multiple pre-clinical models of Huntington disease. • The explanation of the machine learning/AI approach was somewhat difficult to follow.
GWG Votes	**Is the project feasible?**
Yes: 13 **No:** 0	• Yes, the project is feasible and has a high probability of meeting the outlined milestones. • A panelist highlighted the good preliminary data. • Overall, the project appears well-planned, with reasonable activities meeting necessary pre-IND objectives. • Yes, the project is feasible and has a high probability of meeting the outlined milestones.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13 **No:** 0	• Yes • Adequate

Application #	TRAN1-16943
Title (as written by the applicant)	Invariant natural killer T cells expressing a chimeric antigen receptor for clinical use
Translational Candidate (as written by the applicant)	Chimeric antigen receptor invariant natural killer T cells for the treatment of patients with B cell malignancies.
Area of Impact (as written by the applicant)	Use of allogeneic 'off the shelf' CAR based immune cells at lower cost, more readily available and at potentially lower toxicity
Mechanism of Action (as written by the applicant)	The CD19 CAR iNKT cell product has intended both direct cytotoxic function and expanded activity through the activation of the host immune system and the generation of a CD8 mediated host immune response directed against the patients cancer. This product is intended to be more readily available at the time of clinical need, avoid costly single patient manufacturing and to not cause prolonged B cell aplasia.
Unmet Medical Need (as written by the applicant)	Currently there are no 'off the shelf' allogeneic CAR cell products that are available at the time of clinical need. This product would avoid the costly and time consuming requirement of individual manufacturing of current products. Further, it is expected that the CD19 CAR iNKT cells will have reduced toxicities, both related to CRS and ICANS but also avoiding the B cell aplasia of current CD19 directed CAR T cell products.
Project Objective (as written by the applicant)	Pre-IND meeting for use of CD19 CAR iNKT cells.
Major Proposed Activities (as written by the applicant)	• Evaluate iNKT cell content from normal donors • Isolate iNKT cells from apheresis products • Assess purity of iNKT cells for ex vivo expansion • Optimize conditions for INKT cells expansion under GMP compliant procedures • Assess purity and fold expansion • Evaluate frozen and thawed cells • Assess phenotype, cytokine production and gene expression profile of the expanded iNKT cells • Evaluate function of expanded iNKT cells • Utilize CD19 lentiviral CAR vector, assess and optimize transduction efficiency • Assess cytotoxic function in vitro and in vivo in lymphoma model • Develop IND materials and pre-IND package • Prepare for pre-IND meeting with the FDA • Schedule pre-IND meeting with the FDA
Statement of Benefit to California (as written by the applicant)	Many patients in the State of California suffer from B cell malignancies including ALL and non-Hodgkin's lymphoma. CAR T cell therapies are widely offered as potentially curative therapy including at Stanford University. However, the high cost of therapy, logistical issues and toxicity limits efficacy. Our proposal will focusing on improving these therapies to provide an 'off the shelf' allogeneic CD19 CAR iNKT cell therapy to address these concerns for the benefit of California residents.
Funds Requested	$6,130,982
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	6
Highest	90
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	2

Key Questions and Comments

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/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 proposed product will be used in patients with B-cell malignancies who failed anti-CD19 therapy, including chimeric antigen receptor therapy (CAR-T). Even though there may be some options available for patients relapsed after anti-CD19 CAR-T therapy (depending on the nature of the relapse), overall, it represents unmet medical need. • However, the pipeline of competing technologies (including allogeneic approaches) for relapsed B-cell malignancies post-CAR-T therapies, is very dense. The market size could be very tiny if the technology's development is successful. • Fundamental work, which could be done if the project is funded may have a bigger impact as a platform technology with potential use in multiple oncology indications. The therapeutic value of invariant natural killer T (NKT) cells is not well studied and only a few clinical trials are ongoing. • Advantages here are ability to treat with graft versus host (GvH) and graft versus leukemia (GvL) with a single therapy and ability to elicit secondary immune response without B cell aplasia. • There is a significant unmet need to improve CAR-T therapies using an allogeneic approach. However, the development path in this application could benefit from more clarity. Although multiple potential clinical trials are mentioned, a more focused and detailed plan for the primary indication would improve overall planning and regulatory success.
GWG Votes	**Is the rationale sound?**
Yes: 13 **No:** 0	• The scientific rationale is sound. Interestingly, allo-iNKT cells are short-lived and the major mechanism of action is activation of host CD8 cells. Besides low persistence, it provides survival benefit in the mouse model. • Preliminary data presented in the proposal support the rationale. • With the very low frequency of iNKT (0.1-0.5% in circulating blood of adults), it will be hard to produce a large batch with 1000s of doses. The max expansion rate mentioned in the application is 500-600x. It translates to the detailed study of batch-to-batch (donor-to-donor) variability and careful selection of the donor. It will be interesting to see a discussion about alternative sources of iNKT cells, such as bone marrow (mentioned in application as a richer source), cord blood and iPS cell lines.

	• In pre-clinical models the applicant demonstrated that murine iNKT cells have both immunoregulatory and cytotoxic function against B cell malignancies which is important for suppressing graft vs host disease (GVHD) yet allow for the beneficial graft vs tumor (GVT) effect. They show that iNKT cells are approximately 50x more potent than CD4+CD25+FoxP3+ regulatory (Treg) cells in the same murine models. They showed that CD19 CAR iNKT cells have both direct and indirect cytotoxic function in preclinical murine models against CD19 expressing B cell tumors. The indirect function of CD19 CAR iNKT cells can only be demonstrated in immunocompetent animal models as these cells induce an immune response mediated by host CD8 T cells that provides long term anti-tumor benefit. This is important because CD19 CAR iNKT cells do not need to persist. Also show that these animals do not develop prolonged B cell aplasia yet maintain impressive immune mediated rejection of CD19+ malignancies. • The rationale that persistence of the allogeneic CAR iNKT cells isn't required seems counterintuitive, given prior experience with traditional CAR-T therapies. However, the idea that these cells could prime CD8+ T cells to take over the tumor-fighting response after CAR iNKT cells are cleared is intriguing. • Pre-clinical data suggest that animals treated with allogeneic CD19 CAR iNKT cells show prolonged survival compared to those treated with allogeneic CD19 CAR-T cells. They attribute this benefit to the activation of host CD8+ T cells. Questions remain about the durability of the CD8+ response and how this immune "hand-off" consistently works.
GWG Votes	**Is the project well planned and designed?**
Yes: 12 **No:** 1	• The project is well designed. • The applicant will isolate, expand, characterize iNKT, transfect with CAR and pursue CMC product development before IND application. • The proposal includes all necessary activities to meet the program objectives, including preparation for pre-IND meetings with the FDA.
GWG Votes	**Is the project feasible?**
Yes: 13 **No:** 0	• The proposed milestones look feasible. • Strengths include bidirectional effect of iNKT in post-transplant setting, preventing GvH while addressing GvL and use as an allogeneic product. Challenges include scale up synthesis of rare cell population and competitive space around CD19 therapies. • While the therapeutic space for B cell malignancies is crowded, the team hasn't fully addressed how they will navigate this competitive landscape, which could be a potential risk in clinical development. • The proposed milestones and timeline seem feasible and reasonable.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13 **No:** 0	• Yes. • The project upholds principles of Diversity, Equity, and Inclusion (DEI).

Application #	TRAN1-16956
Title (as written by the applicant)	Hypoimmunogenic iPSC-derived TCR-NK cells for oncology
Translational Candidate (as written by the applicant)	Hypoimmunogenic iPSC-derived TCR-NK cells
Area of Impact (as written by the applicant)	NK drug product homogeneity and engraftment/response durability in cancer patients will be improved by this hypoimmunogenic iPSC-TCR-NK cell therapy
Mechanism of Action (as written by the applicant)	The MoA of the candidate involves engagement of cancer-specific antigen peptide-HLA molecules presented on the surface of tumor cells in tissues by the cancer antigen-specific TCR on the iPSC-TCR-NK cells, and subsequent NK activation, degranulation, & killing of tumor cells, and extension of patient life. iPSC-TCR-NK cells are additionally engineered to 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 BCMA-directed therapies. The outcome of relapsed/refractory MM, especially the triple-class refractory patients, (refractory to proteasome inhibitors, immunomodulatory drugs, and anti-CD38 monoclonal antibodies) is dismal. They have an overall response rate of ~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 edited iPSC generation • GMP edited iPSC master cell banking • GMP iPSC-TCR-NK drug product manufacturing • Animal studies (efficacy & pilot safety) • In vitro hypoimmunogenicity testing of GMP drug 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 with high unmet medical need by enabling increased access to effective cancer cell therapies close to home.
Funds Requested	$4,100,845
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	84
Median	87
Standard Deviation	10
Highest	90
Lowest	60
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	12
(1-84): Not recommended for funding	2

Key Questions and Comments

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 12 **No:** 1	• Despite the approval of chimeric antigen receptor T-cell (CAR-T) therapy and monoclonal antibody (mAB) products for multiple myeloma (MM), the disease is still considered incurable due to the high rate of relapses. However, it remains unclear from the Target Product Profile (TPP) if the MM patient population represents an unmet medical need. Current commercial anti-BCMA CAR-T products are indicated for patients with relapsed/refractory (r/r) MM in the 5th line of therapy or beyond. With commercial CAR-T products now moving into the 2nd and 3rd lines of r/r MM therapy, the targeted patient population and its size are uncertain. However, this could be clarified in the next round of funding (CLIN). • The product's value proposition lies in its allogeneic, off-the-shelf nature. All benefits of off-the-shelf allogeneic products are well outlined in the application. Nevertheless, the value proposition for r/r MM patients is currently unclear, as there are already numerous therapeutic options available. Still, as mentioned in the application, the project is indication-agnostic, focusing heavily on CMC activities. • This is a resubmission due to a change in project ownership; it received a high score of 90 in a prior review. This grant was originally recommended for funding to a for-profit company under the same PI, but now resides with a new non-profit institution. • The current proposal remains impactful and is further strengthened by (i) new data demonstrating that induced pluripotent stem cell-derived natural killer cells (iPSC-NKs) generated with the GMP iPSC line and NK differentiation process used in the application yield more durable anti-tumor efficacy and (ii) new team members. • The proposal outlines a path to clinical application for iPSC-derived allogeneic NK therapeutics, with potential implications for treatment cost and accessibility. • There remains significant unmet medical need in regards to MM despite progress in the development of therapeutics for its treatment. • NY-ESO T-cell receptor gene-modified T (TCR-T)-cell therapy has previously been applied in the clinic for MM, so the concept of this proposal is not new.
GWG Votes	**Is the rationale sound?**
Yes: 12	• The scientific rationale is sound. • The preliminary data presented in application are sufficient.

No: 1	• Allo TCR-NKs have a multitude of advantages over autologous TCR-Ts from the efficacy, safety, cost, manufacturing logistics, and patient accessibility perspective. The applicant shows strong data supporting the advantages of hypoimmune iPSC-derived TCR-NKs as a platform for broader use including in solid tumors. • The applicant has shown that iPSC-TCR-NK cells expressing two key immune inhibitory proteins can evade NK, macrophage, and T cell killing and are hypoimmunogenic. • This is a well-planned program based on robust preliminary data that de-risks the approach. • It's unclear why iPSC derived NK cells expressing NY-ESO specific TCR will be more impactful and effective compared to autologous NY-ESO-1 specific autologous T cells. There is no benchmarking data in any of the pre-clinical studies shown in the application.
GWG Votes	**Is the project well planned and designed?**
Yes: 13 **No:** 0	• The project is well planned. • The design is a strength; no concerns. • It looks like applicants have a good understanding of FDA requirements for development of such therapeutic candidate. • A clear path to GMP manufacture is outlined. • The application shows clear understanding of regulatory requirements and steps necessary to meet them.
GWG Votes	**Is the project feasible?**
Yes: 13 **No:** 0	• The timeline and milestones look reasonable. • The team is qualified to perform the work. • Milestones are appropriate and clearly laid out; six primary activities are clear and appropriate including alternatives. There has been no FDA correspondence to date, but there is a clear plan for pre-IND. The project is ready to commence once the notice of grant award (NGA) is signed and initial funds transferred (early spring 2025). • This is a well-planned program with appropriate risks assessment and mitigation strategy.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13 **No:** 0	• Yes. • Despite the translational nature of the project, the applicant provides a clearly defined DEI section including enhanced accessibility, use of patient advocates in future, access, education and clear need within patient population overrepresented by underrepresented patients. • DEI was appropriately considered in the application.

Application #	TRAN1-17000
Title (as written by the applicant)	GlyTR2 CAR T cell translation: safe pan-cancer killing via velcro-like density-dependent targeting of cancer glycans
Translational Candidate (as written by the applicant)	GlyTR2 CAR T cell
Area of Impact (as written by the applicant)	Refractory/metastatic solid cancer
Mechanism of Action (as written by the applicant)	Genetically engineered T cell express a lectin-based chimeric antigen receptor that utilizes high-avidity velcro-like binding to high-density tumor associated glycan antigens to kill a wide diversity of cancer cell types while ignoring normal cells with lower target glycan density to prevent 'on-target, off-cancer' toxicity.
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 and safe pan-cancer therapy for patients with refractory/metastatic solid cancers.
Funds Requested	$4,581,144
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	1
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	• Yes, the cancer indications being pursued in this application represent a class of diseases with unmet medical need. • Compelling, high medical need and translatability that could serve as a platform for other indications: GlyTR2 CAR T cells can uniquely utilize high-avidity velcro-like lectin binding, rather than high-affinity key-lock antibody binding, to target cancer cells (target-density dependent binding such that high target-density cancer cells are killed while low target expressing normal cells are ignored). • If successful, the application could have significant benefit as it identifies a novel target/binder pair that has the potential to be therapeutically relevant across a range of cancer indications.
GWG Votes	**Is the rationale sound?**
Yes: 12 **No:** 0	• The target of the CAR T efforts is novel and the overall rationale underpinning this proposal is sound. • This product represents a critical advantage over CARs that utilize antibodies and is unlikely to cause on-target off-tumor toxicity. • Compelling preliminary data, strengthened in this submission. • The approach to regulatory interactions should be strengthened. The developers should look to bring regulatory expertise in CAR T development into the team. • The use of basket trials for antigen specific therapies is common. However, the applicants do not outline how they will adapt this approach for their basket trial (given the novel nature of the target).
GWG Votes	**Is the project well planned and designed?**
Yes: 12 **No:** 0	• Overall, the project is well planned and well designed. • Clear design and manufacturing plan, including optimization and scalability. • Good preliminary data. • Milestone 6 contains key experiments to inform the briefing package for the pre-IND. Notably, the plan to screen primary and iPSC derived lineages. Use of organoids may be confounding as many CAR T do not infiltrate these structures. • The applicants are correct that there are drawbacks to the use of lentivirus in CAR T manufacture. The applicants do not clearly demonstrate that the use of the 'safe harbor' locus is required. Given the complexity of the process there are concerns around its commercial viability.
GWG Votes	**Is the project feasible?**
Yes: 12 **No:** 0	• Yes, the milestones are reasonable and achievable within the timelines proposed for this project. • There are clearly defined milestones, including troubleshooting. • Based on the strong preliminary data there is clear support for this approach as a therapeutic strategy.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12 **No:** 0	• Overall, the principles of DEI and the plan look reasonable. • Adequate. Discuss further defining enrollment goals for underrepresented racial and ethnic, focusing on barriers to enrollment, discuss a CSW in future. • Yes.

Application #	TRAN1-16994
Title (as written by the applicant)	A gene therapy for the treatment of congenital lipodystrophy
Translational Candidate (as written by the applicant)	This product is being developed as a gene therapy to instruct the patient's own body to manufacture native human leptin as a hormone replacement therapy.
Area of Impact (as written by the applicant)	This product is being developed to treat Congenital Generalized Lipodystrophy (CGL), a genetic disorder causing leptin deficiency and severe metabolic diseases.
Mechanism of Action (as written by the applicant)	We intend for this gene therapy to be dosed every six months. The current treatment, metreleptin, is a synthetic human leptin that can correct for leptin deficiency but is structurally different from native leptin leading to neutralizing leptin antibody production in patients. Also, it's a daily injectable and is associated with significant injection site reactions. A gene therapy allowing the patient's own body to make native leptin will significantly improve CGL patients' standard of care.
Unmet Medical Need (as written by the applicant)	Despite the availability of metreleptin, there are still unmet medical needs for patients with CGL. Metreleptin is a daily injectable that has been associated with significant injection site reactions and the development of anti-leptin antibodies due to its structural differences from native leptin. A gene therapy delivered every six months with native human leptin will address the current unmet medical needs in treatment and make the therapy more patient-centric.
Project Objective (as written by the applicant)	Pre-IND FDA meeting, submission and confirmation
Major Proposed Activities (as written by the applicant)	• Analytical development and testing • Develop and qualify methods for identity, purity, efficacy and quantification • Master Cell Bank (MCB) and Working Cell Bank (WCB) establishment • Establish and characterize E. coli MCB and WCB using clean room facilities • Dose ranging and maximum tolerated dose (MTD) determination • Dose ranging assessment in two different lipodystrophy mouse models • Determination of MTD • Biodistribution and kinetic studies • Determine biodistribution and histopathology • Determine kinetic expression of product components • Head to head assessment of the product and Metreleptin • Assess product directly against the current accepted treatment in mice • Initiate INTERACT and pre-IND meetings • INTERACT meeting to be initiated at the start of the program • Pre-IND to be initiated
Statement of Benefit to California (as written by the applicant)	As a California company, we will advance gene therapy for diseases like the rare disease lipodystrophy, an important but often overlooked disease, using its state-of-the-art platform technology. Establishing California as the industry leader in gene therapy and a Center of Excellence for rare disease treatment will attract talented scientists, boost the California economy, and improve the quality of life of patients and families.
Funds Requested	$4,000,000
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

Process Vote	*All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG."* *Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."*

Scoring Data

Final Score: 85

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

Mean	85
Median	85
Standard Deviation	3
Highest	88
Lowest	75
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	2

Key Questions and Comments

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/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 product is a gene therapy approach delivering human leptin for the treatment of congenital generalized lipodystrophy. CGL is a rare disorder caused by mutations in the Leptin gene. The disease is characterized by the near total loss of adipose tissue associated with metabolic complications related to insulin resistance, such as severe diabetes and hypertriglyceridemia. Current treatment includes daily injection with leptin (Metreleptin a synthetic leptin analogue) which is burdensome, causes injection site reaction and some individual become non-responders because they developed anti metreleptin antibodies. By providing a treatment that could be delivered less frequently (hopefully twice a year rather than daily) and which uses the native protein, it is expected that individuals will be more compliant and achieve better treatments, addressing this unmet need. • This approach would be welcomed by patients with CGL as well as health care providers, as the major issues associated with current treatment (Metreleptin) are linked to the need to perform daily injections. It is also expected that the native protein would prevent the development of neutralizing anti-leptin antibodies (an issue for some Metreleptin non-responders). • There is an approved therapy but it required daily injections, so an unmet need remains. • Providing a more durable and redosable gene therapy would be a big improvement. • Dosing every 6 months would be a major improvement for patients. • This product will accelerate the development of gene therapy for CGL and in addition, the technology used could be used to deliver other cargos for other diseases, as the data show low immunogenicity and broad distribution.

	• The applicant plans to demonstrate initial proof of concept in the context of leptin deficiency but wants to ultimately develop this as a genomic medicine delivery platform for other genetic disorders. • Very rare disease.
GWG Votes	**Is the rationale sound?**
Yes: 11 **No:** 1	• The project is based on a sound scientific rationale, the company has strong preclinical data recently published in a high impact journal.The innovation of this approach is the development of a novel delivery platform for nucleic acid medicines that overcomes the limitations of current delivery systems. This new platform can effectively deliver gene therapies into a wide variety of cells and tissues with low immunogenicity and broad distribution throughout the body. As such, the technology holds promise to revolutionize gene therapy approaches. • The rationale for this application is supported by strong pre-clinical data and by the fact that the same technology has been approved by Health Canada for a clinical trial delivering a vaccine for a different indication. • The major strengths of the application include the novel delivery approach, and the fact that this has been tested in both mice and large animal models and seems to be effective in all models tested to date. Additional strengths of this application include the overall coherence of the proposed project plan, the clinical and manufacturing capabilities of the team. The applicants have outlined a reasonable path to achieving their goal of a pre-IND meeting within 30 months of starting the project. • The genetic basis for CGL is clearly established, and correction of disease has also been shown with a different approach. • Data was provided to support some safety, re-dosability, and minimal neutralizing antibody response. • This is an interesting approach and the applicant has demonstrated that the product can effectively be delivered. • The data supports the development of the product and the applicant has all the equipment and facilities, including GMP facilities to develop the product.
GWG Votes	**Is the project well planned and designed?**
Yes: 12 **No:** 0	• Yes, overall, the project is well planned and well designed and should be achievable within the proposed timeline. • To properly evaluate the platform as a genetic therapy for CGL, the applicant is proposing to move forward with conducting a number of pre-clinical studies to evaluate efficacy and safety including, dose ranging, repeat dosing, biodistribution, and pharmacokinetic studies, as well as a head-to-head study evaluating their product against the current leptin therapy, metreleptin. • The team has identified the key activities and has contingency plans in place to move to the necessary meetings. • One outstanding question is whether antibodies against the protein could hinder efficacy in humans. The team has shown in their pre-clinical study that some of the mice that received the product developed antibodies, but the company concluded these were not neutralizing antibodies. Monitoring for antibodies should be included into their work package. • This is a well-constructed program. However It was slightly unclear why certain doses were used in some activities and the order of activities. For example, in the pilot pharmacology and dose-finding studies, the activity looking at dose and/or schedule optimization should be performed before the *in vivo* studies looking at the different routes of administration. • Overall yes, but the approach for understanding biodistribution is unclear. Multiple methods were listed but the plan appears undeveloped. • Underdeveloped bio-distribution plan. • An INTERACT meeting was listed as a risk mitigation but it's not clear what would trigger whether to pursue this meeting.

GWG Votes	Is the project feasible?
Yes: 11 **No:** 1	• Yes, overall, the project seems feasible. • The project is extremely feasible, as the team has already performed preclinical studies and has experience with Health Canada for delivery of a different cargo using the same platform. • The team has the experience and state of the art facility to perform all the activities. They have enlisted consultant to move to the next steps and are planning to connect with patient registry around the world. • The team has labs and manufacturing facilities both in California and Canada. • The contingency plan seems appropriate, personnel and animal shortages are been mitigated by having personnel with duplicate skill sets and the use of two independent animal models. • Yes, however the dosing approach (frequency and route of administration) is not yet established, which could cause delays.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 8 **No:** 4	• CGL is a rare disease and it has been reported in individuals of every ethnic group without a specific gender bias. The applicant plans to partner with known centers of excellences where these patients are typically treated to help better characterize the patient population. • By developing tools to ensure early diagnosis and treatment, it is expected that overlooked patients (typically low socioeconomic status) will receive better treatment. • The applicant will work with a named Patient Diversity Consultant to help create a Diversity Plan for patients with lipodystrophy. • California will benefit from available registries and therapies as there are patients known to have CGL in the state. • The team does not have a plan to engage with patients to incorporate their perspective and experience. • Limited patient engagement. • The major weakness of this application is some of the scant details related to the large animal and pre-clinical mouse studies. However, a deeper dive of the high impact publication cited in their proposal helped to answer many of the points mentioned in the application. Another weakness is their DEI plan, it is essentially non-existent. They plan to put together a diversity plan for the relevant patient population by bringing onboard a Patient Diversity Consultant. The overall DEI plan is under-developed and not completely thought through in this project. • The plan provided was very limited.

Application #	TRAN1-16986
Title (as written by the applicant)	Development of an off-the-shelf iPSC derived CAR T cell therapy for the treatment of solid tumors
Translational Candidate (as written by the applicant)	Highly engineered iPSC-derived CAR-T cell targeting MICA/B for the treatment of solid tumors without the need for lympho-depleting chemotherapy.
Area of Impact (as written by the applicant)	As a centrally manufactured & highly engineered iPSC-derived cell therapy, this product will be available off-the-shelf & on-demand for solid tumor patients.
Mechanism of Action (as written by the applicant)	With a (i) chimeric antigen receptor that recognizes a unique and conserved domain of MICA/B and (ii) a high-affinity and non-cleavable version of CD16 that can combine with therapeutic ADCC enabled antibodies, this product will be capable of broad and indication-agnostic anti-tumor activity. Additional engineered elements will allow for administration in the absence of lymphodepletion address and enhanced solid tumor activity.
Unmet Medical Need (as written by the applicant)	This product offers a radically different approach to costly and bespoke precision medicine and is intended for broad and universal application across solid tumor indications. It has the potential to be a true off-the-shelf and affordable pan-tumor targeting therapy that is widely available to meet the unmet need in solid tumors across all racial, ethnic, and socio-economic backgrounds.
Project Objective (as written by the applicant)	Pre-IND meeting/discussion and preparation for IND
Major Proposed Activities (as written by the applicant)	• Engineering, banking, and characterization of master cell banks for manufacture. • Selection of master cell bank for manufacture. • Development of identity, characterization, and potency assays. • Transfer of differentiation protocol to manufacturing in preparation for clinical manufacture. • Finalization of Clinical plan. • Preparation for Pre-IND meeting and preparation of IND submission documents.
Statement of Benefit to California (as written by the applicant)	The unique and innovative features incorporated into this product will allow for (i) indication-agnostic anti-tumor efficacy (ii) and broad and on-demand patient access to help overcome the urgent and unmet clinical needs of solid tumor patients in California. The ability to provide a cost effective anti-tumor therapy with potential use in community hospitals will significantly reduce the financial burden of treatment and lead to improved access to treatment options for patients in underserved areas.
Funds Requested	$4,000,000
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***
Process Vote	*All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG."* *Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."*

Scoring Data

Final Score: 85

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

Mean	84
Median	85
Standard Deviation	5
Highest	88
Lowest	70
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	11
(1-84): Not recommended for funding	3

Key Questions and Comments

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 12 **No:** 0	• The impact of the product would be exceptional. Current cellular immunotherapy products lack sufficient activity against solid tumors which comprise 90% of cancer diagnoses. A pan-tumor cellular immunotherapy would have significant impact. • Solid tumors remain a highly unsolved medical problem. • The applicant noted solid tumors comprise over 90% of all new cancer cases and all cancer related mortality. The proposed product would likely impact an unmet medical need if it can demonstrate a suitable anti-tumor efficacy including a persistence with immune evasion. • The value proposition is very strong. While developing cellular immunotherapies to treat solid tumors is challenging, the approach is solid and the reward is high. • A novel chimeric antigen receptor (CAR) that evades immune responses would increase the likelihood of developing a successful product. If the product works as proposed, where immune response evasion with anti-tumor activity is persistent, then it would certainly offer a sufficient value proposition for the health care community. • The allogeneic nature of this therapy has the promise to significantly reduce manufacturing costs, further improving the value proposition to patients and health care providers. • An off-the-shelf approach would be a leap forward for the field. • The CMC activities in this project represents a critical step in advancing a very promising preclinical product to clinical trials. The likelihood of success is high. • Big target patient group.
GWG Votes	**Is the rationale sound?**
Yes: 11 **No:** 1	• The technical rationale for the product is very strong. The investigators provide compelling design of the candidate to address challenges associated with allogeneic cell therapies to treat solid tumors. • Data supporting efficacy of the candidate are strong. These include demonstrating activity of primary CAR-T cells targeting MICA/B in a variety of solid and liquid tumors *in vivo*. Data also supports the use of other edits to improve T cell expansion, activity, and use in ADCC.

	• The data provided supports the use in multiple tumor types and data was provided supporting most of the synthetic edits. • The data clearly supports advancement of the product to clinical evaluation following the CMC activities described in the proposal. • *In vivo* preliminary data is good. • The proposed project does offer a suitably sound scientific rationale. Overall, the rationale includes targeting MHC class proteins that follows a cells oncogenic transformation from stress, an approach for elimination of activated T/NK cells, and the prospectus to circumvent current editing challenges such as transgene size and number of editing steps. • The body of data, including the in vivo studies, does support the scientific rationale to a minimal extent. The *in vitro* data provided to demonstrate the synergy of the edits to resist allogeneic responses for proof of concept of the product may be limited in supporting further development. The charts represent a potentially underpowered two independent donors that constitute the data sets of the co-culture to support allogeneic resistance. A tabulated data set would be more informative to understand the range/error of the two donors. • The product is very complex (multiple engineering steps), but the rationale provided was supportive. • The complexity of the product (number of edits) has the potential to complicate manufacturing and understanding of the effects of the product in various patients and cancer types. • iPSC derived T cells have not demonstrated efficacy in solid tumors. It's difficult to see why this product will succeed where others have failed.
GWG Votes	**Is the project well planned and designed?**
Yes: 12 **No:** 0	• Overall, the project is well planned and designed and has a high probability of achieving the pre-IND milestone within the defined timeframe. • Based on the project plans, all of the activities necessary to meet the program objective to support a pre-IND interaction and subsequent IND filing. • The timeline demonstrates an aggressive sequential approach for all the project's activities. All activities proposed are essential to the project and do demonstrate strategies consistent with CIRM's expectations. • The activities are consistent with moving to a pre-IND meeting. • The consideration of assays for cell identity, characteristics, and activity are well-designed. • The manufacturing methodology (master cell bank, clonal selection, etc.) is logical. • No additional animal studies are proposed prior to the pre-IND, though preliminary data is likely sufficient. • The program is constructed with some concerns. It seemingly has appropriate elements consistent with the principles of quality by design but the proof of concept data is limited. • There is a lack of sufficient detail in the methodology of editing and differentiation. Both of these are challenging. The team has shown the capability to do so but it is difficult to evaluate how their methods will translate at scale for manufacturing.
GWG Votes	**Is the project feasible?**
Yes: 12 **No:** 0	• Qualitatively the milestones are appropriate and likely to be achieved. • The team is outstanding with expertise in all aspects of candidate development and manufacturing. • There is risk with likely success. • The applicant's team is appropriately qualified, sufficiently staffed, with the inclusion of suitable designated team leads for the interactions across departments. • Overall, the project is feasible from a technical and clinical perspective. From a biology perspective, it's difficult to believe that this will actually make an impact for solid tumor indications.

	• Milestones proposed have a moderate to high risk of not being achieved on time, however the other expected outcomes have a low risk overall of not being able to achieve the expected project outcome. • The team has access to the necessary resources to conduct the proposed manufacturing activities. There are no concerns for any resources to achieve the objectives expected, other than the risk of insufficient time. • There are three manufacturing risks identified by the applicant as needing contingency plans. If issues were to arise, the project's back-up plans are viable to support maintenance of the master cell bank (MCB) and Drug Product, generation of the MCB in the event it does not produce viable clones, and advancing the risk surveillance/characterization to support MCB iPSC differentiation if it is compromised. • Apparent risks to this program are identified in the proposal for a product at this stage of development. There is an eventual concern that demonstrating control for one of the product's functional attributes, allogeneic resistance, will need additional development for its assessment. • Quantitative milestones would improve the proposal. For example, it is unclear what manufacturing scale is needed and what values the assay benchmarks should achieve. • One concern was that no real risks were identified other than the need to have frequent meetings to ensure there are no delays.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12 **No:** 0	• The project plan does adequately address for exclusive influences with a plan to broaden the reach, and gather diverse perspectives on all aspects pertinent to their drug product by engaging with clinical experts, with site engagement activities, and including the patient community. • Considering they describe the disease burden for some cancers, including endometrial cancer that impact California with significantly higher increase in mortality rates in non-Hispanic black women compared to other ethnicities, the project information outcomes would likely serve the unmet medical needs of the California population. • The applicants goals do include approaches to incorporate perspectives with plans to engage directly with potential patients/advocacy groups. Their effort is intended to "provide feedback from groups most impacted by the disease." • The plan tests the candidate on mice of different sexes and against cell lines of cancers from patients with different race and ethnicity. • The team works to engage diverse sets of clinicians, patients, and community members in their product development strategy. • Minimal plan provided.

Application #	TRAN1-16912
Title (as written by the applicant)	Next-generation, Cytokine-armored CAR-T Cell Therapy for Glioblastoma
Translational Candidate (as written by the applicant)	An IL-13Ra2–targeted CAR-T cell therapy armored with inducible IL-12 and IL-18 secretion will be studied for the treatment of glioblastoma.
Area of Impact (as written by the applicant)	Glioblastoma is an incurable disease with extremely poor prognosis. Successful execution of this project will provide a new therapy for glioblastoma.
Mechanism of Action (as written by the applicant)	The proposed candidate is a CAR-T cell therapy with two distinct features. First, the CAR directly recognizes IL-13Ra2, which is a protein on the surface of GBM cells that allows the CAR-T cells to directly target and kill the tumor cells. Furthermore, the IL-12 and IL-18 secreted by the CAR-T cells can recruit and activate the body's native immune response against the tumor, providing reinforcement that further enhances the overall efficacy of the CAR-T cell therapy.
Unmet Medical Need (as written by the applicant)	Glioblastoma is the most common form of primary brain tumor among adults, with a five-year survival rate less than 7%. Aggressive chemotherapy, surgery, and radiation prove insufficient to achieve durable tumor control for the vast majority of patients. A small number of patients have responded to CAR-T cell therapy, but the overall response rate remains low and responses are typically short-lived, highlighting a need for next-generation designs that can overcome tumor resistance mechanisms.
Project Objective (as written by the applicant)	To conduct a pre-IND meeting with the FDA.
Major Proposed Activities (as written by the applicant)	• Finalize clinical-grade cell-manufacturing protocol and demonstrate successful cGMP cell manufacturing • Demonstrate efficacy and safety of the Therapeutic Candidate in multiple human GBM xenograft models • Evaluate the potential for combining the Therapeutic Candidate with systemic or locoregional anti-VEGF antibody therapy for GBM • Complete clinical protocol development and regulatory preparation for pre-IND meeting
Statement of Benefit to California (as written by the applicant)	Glioblastoma accounts for close to half of all brain-tumor cases, and the annual incidence in the United States is estimated at 3.26 per 100,000 people. The median survival for newly diagnosed patients receiving standard of care is only 12–15 months, and the survival rate 5 years post-diagnosis is less than 7%. For decades, GBM survival rates and mortality statistics have remained unchanged. New treatment options with greater long-term efficacy are urgently needed.
Funds Requested	$5,216,915
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	89
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	9
(1-84): Not recommended for funding	6

Key Questions and Comments

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/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:** 1	• This product would impact an unmet medical need. Glioblastoma (GBM) has an abysmal survival rate and causes significant morbidity and mortality among those impacted by it. Existing treatments include chemo, radiation, and surgery however the median survival is approximately 12-15 months. • The process for this product's development is likely suitable to support potential treatments for glioblastoma based on the appropriately planned progression of research through engineering activities prior to GMP manufacturing. • The proposed product has technically advanced the profile of CAR-T products which should increase the likelihood of improving cell and gene therapy technologies. • There is a sufficient opportunity for the product to provide an impact to patients based on the CMC plans for developing an investigational cell-based therapeutic. • This is well written. There is a real unmet need for GBM. • There are many CAR-T programs being developed today for GBM. Targeting IL-13RA2 is not a novel concept and has been used in the clinic. • If efficacious this product would add a significant treatment option to the existing therapies for patients with glioblastoma. It is impossible to know if this product would lead to long term cures or if it would become part of the treatment options provided to patients as they continue along the path to a bad outcome. If approved, the product is likely to be expensive. Additionally, this type of treatment must be given in specialized centers, possibly requiring patients to relocate for weeks if not months. These issues of direct and indirect (lost wages, childcare costs, travel costs) all enter into discussion of treatment with this product. Ideally improved outcomes would outweigh these costs but these costs will be significant.
GWG Votes	**Is the rationale sound?**
Yes: 11 **No:** 2	• Yes. The rationale builds on prior research targeting IL-13Ra2. It adds inducible interleukin 12 and interleukin 18 to improve anti-tumor efficacy by decreasing the immunosuppressive nature of the tumor microenvironment. The team has non-clinical data supporting this approach.

	• The proposed project has a sound scientific rationale. Overall the approach used to manufacture the research product are consistent with procedures suitable to support the planned advancement into the industrial relevant platforms.
	• The body of data does support the products capabilities *in vivo* but is limited with regard to the *in vitro* data provided to support control of the product. Product specific attributes, such as expression of the transgenes, expression per unit copy number, and percent cells expressed are limited in their description and/or are described as planned to be developed.
	• The data supports development based on the *in-vivo* efficacy of the clinically relevant construct. The *in vitro* data demonstrate efficacy, but questions remain if the applicant will be able to control transduction considering potential cell population variabilities patient to patient.
	• Armored CAR is very important to overcome heterogeneity and immunosuppression. However, data provided does not convincingly achieve this. Pre-clinical data is impressive, but if tumor cells are 100% transfected with IL-13ra, then it's not clear that armored CAR is overcoming heterogeneity. Additional data that this approach will work in models that have some IL13a expression (but not complete) would enhance the application.
	• Two major concerns for this project include:
	  ○ The use of nuclear factor of activated T cells (NFAT) promoter to regulate IL-12 and IL-18 expression in activated T cells. NFAT regulated cytokine expression has been tried in the clinic before. This is a leaky promoter and not specific to activated T cells. Potential systemic toxicity is a major concern. The applicant does not address how they will overcome this issue, from a safety perspective.
	  ○ The second major concern relates to the selected cytokine combination of IL-12 and IL-18. The applicant claims that these two cytokines interact synergistically to increase overall efficacy. But synergy is a byproduct of specific concentrations. Producing both cytokines under control of NFAT does not guarantee that you will get the correct levels of cytokines to maximize overall synergistic potential in GBM.

GWG Votes	**Is the project well planned and designed?**
Yes: 12 **No:** 1	• The proposed activities are designed to optimize safety and efficacy of the product before transitioning to human subjects. The steps described in the application are necessary to ensure such a transition is helpful and not harmful to patients but the described timelines demonstrate urgency. The team is on track for a successful pre-IND meeting. • This is a good team. • The program is well constructed and consistent with quality by design principles. The applicant demonstrates anti-tumor efficacy through repeated challenge cycles, without off-tumor toxicity in a second model, following an appropriate selection process to derive the IL-13Rα2 CAR-T cells with IL12 and IL18. • The proposed activities for analytical development, manufacturing clinical-grade plasmid for pilot and full-scale clinical-grade vector production, and for engineering and qualification runs at the cell product facility all support essential project needs in an appropriate strategy that is consistent with CIRM's mission • The project is well planned and designed but more info and data on how cytokines might be tunable to prevent toxicity would be appreciated. • The project includes all of the necessary activities to meet the program objective. There are descriptions for advancing the rLV to a CDMO/vendor to support the production of the materials to be used in drug product manufacturing for nonclinical and clinical portions of the study, however the product specific testing for the rLV to support controlled transductions with target expression profiles is limited in its descriptions.
GWG Votes	**Is the project feasible?**

Yes: 13 **No:** 0	• The proposed CMC activities for the vector and the cells are planned over an appropriate time frame (expected under 3 yrs). Considering the development and planning to date, the project outcomes are likely to be achieved. • The team is well qualified, including having extensive experience in the specific product's development, and the project's key personnel outline shows suitable staffing to feasibly support the program.. • With access to their institution's human gene and cell therapy facility and the vector core facility at a collaborating medical center, the team has the necessary access and resources to conduct the proposed activities. • The applicant's identified risks and contingency plans are viable to maintain the expected timelines. With the greatest risk to the timelines being availability of vector, the team has plans to use another collaborating institution's vector production facility if their planned partner is unable to provide the appropriate vector. • The project is feasible. • There is a good plan. • This is an experienced team with a proven track record. Their contingency plans seem to manage risks. The largest risk is that the identified therapeutic candidate would need to be replaced for issues related to unexpected/major toxicities. The team estimates that if the candidate needs to be replaced it would delay them by 15 months and $180k. They have not identified funding for this risk, outside of contingency funding for incurred costs associated with virus production.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13 **No:** 0	• Glioblastoma incidence is highest in Caucasian males however it is a disease that impacts all demographic populations. The investigators and treatment centers have a history of recruiting a diverse population of patients both sex/gender and race/ethnicity. • The project plan adequately addresses the principles of DEI with its inclusion and assessment of the indications demographics, including the related health disparities noted across several forms of the disease. • The applicant plans to engage with a clinical-trial coordinator to develop a trial diversity plan following FDA guidance, one of their initial DEI tasks. This will be done with collaborative input from the institution's cancer center's community outreach and engagement unit to help assure the development of a product that serves the unmet medical needs of California. • The applicant plans to engage the communities by providing clinical trial information and informed consent form (ICF) from the proposed trial into the CA population's diverse languages. The applicant has perspectives resulting from years of patient feedback 'from the voices of our racially, ethnically, and culturally diverse patients'. These perspectives and experience are from the population that will benefit from the proposed product. • The project upholds principles of diversity, equity, and inclusion (DEI). • Importantly, underinsured patients with this disease have worse outcomes than patients with insurance. Of note and as mentioned previously it is possible that the development of what is likely to be a costly treatment won't impact outcomes in those patients with limited or no insurance. This is not specific to this project nor can the investigator be blamed for this but it is worthy of note.

Application #	TRAN1-16907
Title (as written by the applicant)	Hematopoietic Stem Cell Gene Therapy for MPSIIIB (Sanfilippo B) Syndrome
Translational Candidate (as written by the applicant)	Autologous hematopoietic stem cells from patients with Sanfilippo Syndrome modified with a viral vector which restores a therapeutic enzyme
Area of Impact (as written by the applicant)	This candidate targets the condition of San Filippo B Syndrome for which there are no currently available treatments
Mechanism of Action (as written by the applicant)	The proposed candidate is a stem cell product manufactured from each patient's own hematopoietic (blood forming) stem cells. Hematopoietic stem cells are collected from the patient, modified using a virus to add a therapeutic enzyme gene, and transplanted back into the patient. Upon engraftment of the stem cells in the bone marrow, the gene-corrected cells deliver a missing enzyme to the brain, effectively curing the disease.
Unmet Medical Need (as written by the applicant)	Sanfilippo B Syndrome is a devastating pediatric neurodegenerative disease with no available treatments. Affected children lose developmental milestones, eventually becoming wheelchair bound and dying before adulthood. Autologous HSC gene therapy (GT) has demonstrated clinical success for the closely related Sanfilippo A Syndrome. A similar HSC GT approach for San Filippo B Syndrome could provide a curative therapy for these patients.
Project Objective (as written by the applicant)	Hold a well-prepared pre-IND meeting with FDA
Major Proposed Activities (as written by the applicant)	• Manufacture clinical-grade virus containing the therapeutic gene • Perform laboratory testing to ensure that virus meets quality and safety standards • Demonstrate at-scale manufacturing of the stem cell product • Perform quality and safety testing • Perform stability studies • Perform a toxicology study of the human stem cell product in an immune deficient mouse model to confirm product safety • Perform FDA-required genotoxicity safety testing of the clinical-grade virus using a specialized assay • Prepare a draft clinical protocol • Prepare study reports • Hold a PreIND meeting with FDA
Statement of Benefit to California (as written by the applicant)	Sanfilippo B Syndrome is a devastating pediatric neurodegenerative disease with no effective therapies. Stem cell gene therapy has been highly effective for similar diseases. Successful demonstration that stem cell gene therapy can safely and effectively cure Sanfilippo B Syndrome will shift the paradigm by which patients will be treated, led by California's position as a leader in the field of gene therapy. This will result in improved patient care in the state and around the world.
Funds Requested	$5,211,756
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	82
Median	85
Standard Deviation	4
Highest	88
Lowest	75
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	8
(1-84): Not recommended for funding	7

Key Questions and Comments

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 7 **No:** 6	• The proposed product is designed to treat the ultra-rare disease Mucopolysaccharidosis Type III (MPS IIIB). There is no treatment for this disease. • MPS IIIB is an inherited autosomal recessive disease defined by loss of N-acetylglucosaminidase (NAGLU) function leading to accumulation of heparan sulfate. Patients experience cognitive loss, behavioral dysfunction, hearing loss, motor function, and eventually become wheelchair-bound during adolescence and dying before adulthood. • The target disease is very rare, limiting its extent. • There is no cure currently available. However, a new product, Tralesinidase Alfa (UK), shows promise. This product fuses NAGLU with insulin-like growth factor-2 (IGF2), enhancing uptake via the IGF2-binding site of the cation-independent M6P receptor (CI-MPR). It has demonstrated some clinical efficacy after intracerebroventricular (ICV) administration. The ongoing clinical trial is set to conclude in February 2025. Even if proven effective, it's important to note that repeated ICV injections would still pose a considerable burden for patients. • In light of these issues, hematopoietic stem cell gene therapy for Sanfilippo seems to be a viable option for a therapy. Success is likely as a similar approach has already been used for MPS IIIA (loss of sulfamidase that also leads to accumulation of a heparan sulfate product), and clinical results have been "excellent" in the 5 MPS IIIA patients treated to date. • This approach would provide long term impact without need for repeated injections. • The applicant already has relevant clinical trial experience with this type of therapeutic approach. Their proposed work is at an advanced stage and can benefit from data gathered from the related clinical program they are developing for patients. Given the level of advancement, this proposal appears more suitable as a CLIN application rather than a TRAN application. • There is an unmet medical need for MPS IIIB, a devastating disease. However, given the ultra-rare nature of MPSIIIB (with an incidence of approximately 1 in 1,000,000 live births, and only 40 cases of MPS IIIB in the U.S over 20 years), clinical development, commercialization and then impacting the broader development of stem cell or gene therapies will be very challenging. • MPS IIIA is more common, with a prevalence of 1 in 100,000 to 1 in 200,000 live births, compared to the rarer MPS IIIB. Since the approach to treating both types is similar,

	proceeding with MPSIIIB before fully learning from MPS IIIA may not offer much new insight.
GWG Votes	**Is the rationale sound?**
Yes: 13 **No:** 0	• The applicant is developing a gene modified autologous hematopoietic stem cell and progenitor cell therapy. The patient's own stem cells are harvested and modified using a lentiviral approach that drives high levels of myeloid specific NAGLU enzyme expression. The idea is that upon transplantation and engraftment of the hematopoietic stem and progenitor cells (HSPCs) into the bone marrow, bone marrow derived monocytes will express and secrete high level of enzymes that can repopulate microglia niche within the brain and enable cross correction within the CNS. • Yes, this work is similar to a related program in the clinic. • The proposed lentiviral gene modified autologous hematopoietic stem cells (HSC) treatment is based on the same vector backbone and promoter as one currently being tested in a phase1/2 trial in a related indication with encouraging preliminary results. The proposed plan is well defined and seems readily achievable. The clinical results from a similar trial as well as the MPS IIIB mouse model data support the scientific rationale. • Trafficking of gene-modified, HSC-derived monocytes into the CNS may provide uniform and durable levels of enzyme expression throughout the brain parenchyma. • The rationale for using the vector in microglia cell lines is demonstrated by its ability to restore both intracellular NAGLU activity and promote the secretion of NAGLU extracellularly. • Data using murine model of MPS IIIB in which the therapeutic candidate is transplanted after myeloablative busulfan conditioning show 80% donor peripheral blood chimerism in the transplant groups after approximately four months. • The therapy builds on a similar platform successfully used in a phase I/II trial, showing promising results in less than ten patients. Pre-clinical testing in MPS IIIB mice also demonstrated therapeutic efficacy. • There is some concern regarding the control's results in the behavioral study.
GWG Votes	**Is the project well planned and designed?**
Yes: 13 **No:** 0	• Yes, in fact, the proposal for carrying out toxicology testing usually occurs after a pre-IND meeting, and there is some risk initiating prior to this meeting. • Overall activities are adequate to meet the program objective. • Details are provided for individual milestones, and investigators and sites of performance have been identified. • The activities outlined in the proposal seem reasonable. However, the plan to focus the clinical trial on a single site at the host institution could severely limit patient recruitment, even at a key center, given the extreme rarity of MPS IIIB. • One FDA requirement for *in vivo* model selection is that for treatment of pediatric patients, evidence of "prospect of direct benefit" (clinically meaningful benefit) from appropriate animal models or adult humans must be provided. However, apart from correction of inflammation, no other functional neurological benefits associated with the product specifically have been shown by the applicant, which could represent an issue for the pre-IND meeting.
GWG Votes	**Is the project feasible?**
Yes: 13 **No:** 0	• The applicant provides good preliminary data in their proposal. • The project appears feasible, particularly the chemistry, manufacturing, and controls (CMC) plan which is straightforward and appropriate. • The applicant team has a suitable readiness plan. All Milestones are feasible. • While the current TRAN activities are feasible, given the ongoing studies for MPS IIIA, concentrating efforts on the even rarer MPS IIIB at a single site could affect patient recruitment.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes:	• The applicant considers DEI as much as possible for an ultra rare disease.

13 **No:** 0	• As an autologous cell product, this therapy would eliminate racial disparities typically associated with allogeneic hematopoietic stem cell transplant (HSCT). • Several activities are planned that incorporate diverse perspectives directly into research project implementation. • The applicant is formally engaged with two organizations which support families living with Sanfilippo disease. • The investigators consider the final cost of product and provide potential avenues for undeserved minority for access (i.e. Medicaid coverage).

Application #	TRAN4-17158
Title (as written by the applicant)	Purpose-built cell engineering for rapid manufacturing of stem-like cell therapies.
Translational Candidate (as written by the applicant)	We will develop a product that consists of instrument and workflows to better manufacture cell therapies by using more rapid production methods.
Area of Impact (as written by the applicant)	The impact will be to reduce extended gene editing time (greater than two days) that results in a decreased stem-like phenotype of cell therapies.
Mechanism of Action (as written by the applicant)	The new tools and workflows will decrease the time needed to genetically modify T cell and HSC therapies, thereby improving the stem-like phenotype of the products and improve product potency. The use will be in various forms of cell replacement therapy in which genetically modified cells that show deleted function (e.g. inhibitors of non-desired activity) or new function (e.g. targeting of cancer antigen).
Unmet Medical Need (as written by the applicant)	The expected outcome is to develop a gene editing platform that effectively and consistently meets the performance goals of rapid cell therapy engineering to create ultra-fit populations of stem-like products. The unmet need for cell therapy developers includes an improved cell product quality, shortening vein to vein manufacturing time, and lowering the cost of goods of products. Current payload delivery is not suitable for rapid manufacturing workflows due to high cell loss.
Project Objective (as written by the applicant)	Readiness for transfer to manufacturing.
Major Proposed Activities (as written by the applicant)	• Design consumable with minimal dead volume for rapid transfection of resting T cells and HSPCs. • Validate the consumable for <6-hour HSPC materials. • Gather customer feedback from selected pharmaceutical companies. • Optimize pre-transfection processes for resting T cell and HSPC workflows. • Optimize transfection processes for resting T cell and HSPC workflows. • Optimize post-transfection processes and fill/finish for resting T cell and HSPC workflows and validate functionality.
Statement of Benefit to California (as written by the applicant)	The applicant organization is a California company with the potential to be the gold standard of rapid manufacturing of cell therapies. The market of cell therapies is several billion dollars, of which we could command a significant portion, estimated at $80 million per commercial asset. Success in the proposed project will position our company and its employees to generate substantial economic impact while also helping California patients afflicted with disease treatable by cell therapies.
Funds Requested	$1,187,250
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	79
Median	85
Standard Deviation	11
Highest	86
Lowest	50
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	8
(1-84): Not recommended for funding	7

Key Questions and Comments

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 12 **No:** 1	• The product would accelerate development of gene edited stem cells by improving the manufacturing process. Specifically, this project will focus on developing an instrument and associated protocols for CRISPR-based knockouts, transposon integration, and CRISPR-based knockins in chimeric antigen receptor (CAR-T) cells and hematopoietic stem cell (HSCs). • The proposed product is likely to impact an unmet medical need. The idea of having a rapid and efficient gene editing system that addresses the limitations of the conventional strategies is compelling. • The proposed instrument will accelerate non-viral gene editing in cell therapies. This would accelerate manufacturing, reduce cost, and perhaps increasing efficacy. • More potent cell therapies, mainly T and hematopoietic stem/progenitor cell therapies, could be advanced by using this tool. • Less toxic protein/gene transfer methods could enable more potent cell therapies. • The value proposition is impactful in accelerating manufacturing time, which is important in delivering autologous therapies to patients. • If the project is successful in making a new cell therapy, it offers a value proposition. • Mechanoporation is a promising method to engineer several types of cells. • The product may also reduce manufacturing costs by reducing time and increasing efficiency of gene delivery. • If successful the product would likely have applications in other ex vivo gene delivery applications. • The project has general applicability. • If they can move this to scale up, then it has a huge value proposition. Even if it doesn't make it to clinical application, it would still have a commercially viable endpoint as a laboratory tool. • There is some concern about integration of this technology into manufacturing workflows. It is difficult to alter existing processes from a regulatory standpoint. A support letter mitigates this concern somewhat, providing a partner to test the technology in CAR-T cell manufacturing.

	• There are many similar products to this one on the market today. It's unclear if there is a major need for this tool.
GWG Votes	**Is the rationale sound?**
Yes: 13 **No:** 0	• The principal idea is to use mechanical forces to transfect quiescent cells without the need for electroporation which results in a predictable loss of cells. • The premise of using mechanical forces to facilitate delivery of nonviral DNA into cells as an alternative to electroporation or chemical poration is compelling. • The mechanoporation strategy is novel and based on sound scientific principles. • The data supports development of the product, i.e., the idea of efficient transfection at the lower scale. • The data at the lower scale support the idea of the expansion. • Microfluidic handling can offer precise and uniform conditions that lead to rapid and efficient large molecule delivery. • The team has demonstrated a proof-of-concept of the rationale with prior work at small volumes in their device. This supports the proposal to scale manufacturing to clinical doses of therapeutic cells. • Data generated by the team demonstrate good transfection and editing efficiency and viability of cells in their device, for both CAR-T cells and HSPCs. • Data demonstrate the ability to edit resting T cells to improve CAR-T knockin and T cell memory phenotypes. • Data show i*n vitro* functionality of cells transfected in the instrument. • The choice of the cell types makes sense. • Payload/gene transfer is well supported by the data in the application. • Direct benchmarking to current gold standard techniques is not provided, except in the HSC knockout. This makes it difficult to assess the extent of improvement of this instrument. • The applicant is under-estimating the engineering challenges.
GWG Votes	**Is the project well planned and designed?**
Yes: 8 **No:** 5	• Device design and characterization are strong. • *In vitro* testing of the cell products is appropriate. • A logical plan is in place for scaling manufacturing to clinical cell doses. • The team identifies appropriate variables for both instrument and protocol optimization, but the proposal lacks a process consistent with quality by design (QbD) principles. The design space is huge and a design of experiments (DoE) approach would help identify optimal critical process parameter (CPPs) for performance. • *In vitro* cell assessment in terms of both transfection/editing efficiency, viability, and phenotypes is strong. • Overall, yes, but this is a complicated path since it is potentially a combination product: device and cell therapy for a specific disease. This needs a CBER communication/FDA consultant to work with the team on how to proceed if this is going to be cGMP cell manufacturing platform and not a research lab transfection platform. • It is unclear whether there was the validation that cells within the channels are exposed to the same mechanical stimuli. The idea behind their technology is that cells are subjected to short compressions that result in opening of membrane pores to induce active transport of target molecules into the cell. The applicant needs to show that this produces a uniform stimulus to all cells via computational fluid dynamics (CFD) or some other similar measurements. Cumulative results are provided in Figures 2-3, but the high-volume (HV) scale-up may not be uniform. • The air pressurization pulse is confusing. If there is a high pressure gas/protein containing liquid interface, then this is prone to foaming. This may be a non-problem, that they don't observe; however, it is common in perfusion systems of biological fluids. • Some things are missing: the specs on the pressure/flow characteristics of the channels, etc. or the tolerances that the stereolithography (SLA) printing yields in their designs.

	Activity 1b seems vague, and the tight seals required may not be amenable to 3D printing and glue. • There is concern around the feasibility of the applicant's plans for the engineering of a scaled system to support later stage market activities. • A side-by-side comparison with an electroporator should be integrated into the plans. • More attention is needed to the fabrication for scale-up and its biocompatibility. • More thorough genomic analysis should be done with the processed cells, including karyotypic abnormalities and off-target profiling. • Lack of benchmarking of this device (and the resulting products) to existing "gold standards" is problematic. • It's unclear if this team has the capabilities or the track record to take this all the way to a device that can be used within the clinical manufacturing setting. • A lack of efficacy and safety using *in vivo* model systems is a limitation in advancing to manufacturing and commercialization. • The lack of benchmarking this device to current gold standards in terms of cell quality is a weakness. • A lack of *in vivo* assessment is a weakness. This is standard and expected for both cell types studied.
GWG Votes	**Is the project feasible?**
Yes: 13 **No:** 0	• The proposed milestones and the expected project outcome are probably achievable within the proposed timeline. • The milestones are clear and quantitative. • The proposed team is uniquely qualified for the project. • This is a well qualified team with all of the necessary facilities and resources. • The team has the expertise to perform the proposed study. • Given the large design parameter space there is some concern about the ability to meet the timeline without a more clear optimization plan. • All necessary resources are available to the applicant organization. • Stem cell expertise is needed. A collaborator is necessary for proper functional studies. • The team should add more biology expertise. • The contingency plan to manage risks and delay is underdeveloped. • VC funding may not be a feasible risk mitigation strategy in the current funding environment.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12 **No:** 1	• The project plan and design adequately address and account for the influence of race, ethnicity, sex and gender diversity. • In the DEI plan the team indicates that they will use samples from diverse groups, although this is not explicitly discussed in the scientific plan. • Improved manufacturing could reduce costs and make therapies more accessible to underserved populations. • This product has the potential to impact development of cell therapies that would meet the needs of all Californians by accelerating the manufacturing of these therapies. • The project outcomes would inform the development of a product that serves the unmet medical needs of the diverse California population. • The applicant incorporate perspectives and experience from the population that will benefit from the proposed product in the implementation of the research project. • The applicant's approach to incorporating diverse perspectives and experience in the implementation of the research project is OK. • The team proposes to hold workshops for potential patient populations and underserved communities. • There is a minor concern about the plans to uphold these principles. • The DEI statement did not provide many plans that uphold these principles.

Application #	TRAN1-16938
Title (as written by the applicant)	iPSC-derived Thymic Epithelial Cells as Novel Cell Therapy for T Cell Reconstitution in Congenital Athymia Patients
Translational Candidate (as written by the applicant)	Functional 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)	We have developed a differentiation platform that derives functional TECs from iPSCs that could dramatically improve treatment options for patients with congenital athymia. With prior CIRM support, we differentiated TEC products from 4 iPSC- and 2 ESC-lines and obtained robust human T cell immune reconstitution in transplanted athymic humanized mice. Here we propose key experiments to progress toward clinical translation for transplant and restoration of thymic function in athymic patients.
Unmet Medical Need (as written by the applicant)	The only available treatment for congenital athymia 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 Duke University Medical Center, 3. HLA-unmatched can lead to poor graft function necessitating continued isolation and causing near 100% incidence of autoimmune complications. Thus, there is a critical need for better treatment options.
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	$6,000,039
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	83
Median	84
Standard Deviation	3
Highest	86
Lowest	75
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	2
(1-84): Not recommended for funding	12

Key Questions and Comments

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 12 **No:** 1	• The product would address a critical unmet medical need. • There is additional benefit for patients in the lack of a requirement for pretreatment therapies. • This is a very rare condition; gene therapy is not often relevant. • The work would meet an unmet need for patients who can't access approved therapies in this space. • Congenital athymia is a life-threatening disorder defined by absence of thymic development and profound T cell immunodeficiency. The only currently available treatment (RETHYMICA) is HLA-unmatched 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. • This proposal aims to apply iPSC-derived thymic epithelial cells (TECs) for cell transplantation therapy. Specially, they propose to develop functional TECs from HLA-matched iPSC lines into a cell therapy for congenital athymia.
GWG Votes	**Is the rationale sound?**
Yes: 12 **No:** 1	• Yes - additional preclinical supportive data were provided in this resubmission. • The team has now explained their plan for HLA-matching and the differentiation has been de-risked significantly. • The rationale is sound. Patients with congenital athymia carry mutations that perturb thymic development in vivo and in vitro, preventing the use of autologous iPSCs, unless they were genetically modified. In the proposal, it mentioned that unmanipulated iPSCs have a better differentiation capacity into TECs over gene-corrected cells. Patients that carry a large deletion (e.g., 22q11 Deletion) are not amenable to gene correction. Therefore, the team pursue an allogenic HLA-matched approach. • This proposal specifically focuses on generating three therapeutic candidate products (3 iPSCs-derived- TECs) from three ethnically diverse donors to demonstrate the robustness of their approach. Two of the candidate products will be matched to two real-life patients of the PI, both of whom experience poor graft function after (RETHYMICA) treatment. • The team have provided data for the differentiation platform and the further optimization to derive functional TECs from hPSCs with improved purity and yield. They also translated the process into a cGMP-compatible differentiation platform. • By differentiating the specified reporter line into TECs, the team confirmed that the frequency of cells expressing the reporter is consistent across repeat experiments with

	different batches of media. This additional data has addressed the previous reviewers' concern of the reagents that would be used for cGMP-grade manufacturing. However, using reporter line cannot really demonstrate the reproducibility of differentiation protocol across new generated iPSC lines. The team has identified these differentiation variations as a moderate risk but do not expect major challenges based on their experience.
GWG Votes	**Is the project well planned and designed?**
Yes: 5 **No:** 8	• This is an improved re-submission; the HLA matching issue is resolved. Post-grant activity is vague. Perhaps starting to recruit patients is premature? • The project is appropriately planned. In the initial review there was confusion about whether the term "HLA-matched" is accurate. The team has now explained their plan for HLA-matching. • Because they will generate TECs from iPSCs, and generate iPSCs from blood cells, their HLA-matching strategy can tap into the resources developed for hematopoietic stem cell transplantation, which is that for patients without a suitable related HLA-matched donor, they can go search in "Be the Match Registry" of the National Marrow Donor Program (NMDP). NMDP has provided letter of support to confirm the collaboration with the team to find the HLA-matched donor cells in future, if the product towards to a clinical trial testing. • There is a >80% likelihood of finding a 7/8 HLA-matched donor, while >99% of all patients from all ethnic/racial groups will be able to find a donor if match stringency is reduced to a 6/8 HLA-match. They therefore propose to strive for an "6/8 or better" HLA-match, which will be feasible in > 99% of patients from all ethnic/racial groups. • From the hematopoietic stem cell transplantation experience of the last 60 years, an 8/8 HLA-match for iPSC-derived thymic tissues will be most desirable; however, a 7/8 match or 6/8 match is beyond doubt far superior in reducing autoimmune complications compared to a 0/8 match which is the current standard of care. • The team has well-addressed the reviewers' questions about the HLA-matching plan. • The proposed activities exceed readiness for a pre-IND and are consistent with the applicant's plan to initiate clinical trials after the term of the grant. In particular, Milestone 5 is out of scope. It is misleading as it is identified as a pilot safety study but in reality would be the definitive safety study. • CMC data and prior experience with the described manufacturing methods needs to be better described. • Some of the program's activities come across as premature, such as patient recruitment, and are not appropriate for the stage of development requested for funding. • More attention is needed on the CMC aspects of the work and less on the more academic aspects of the work. • Patient recruitment activities are generally not in scope for pre-IND activities.
GWG Votes	**Is the project feasible?**
Yes: 12 **No:** 1	• There are 6 milestones focused on in vitro and in vivo validation of 3 iPSC-derived TECs. The project is likely to be achieved. • The work builds on significant prior work on differentiation. • The product's capability of being characterized using RNA sequencing may not be suitable to assure product consistency during later stages of clinical development. • Yes. However, this appears to exceed pre-IND expectations.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**

Application #	TRAN1-16933
Title (as written by the applicant)	Novel CD19 CD20 Dual Targeting Allogeneic CAR-T Therapy in Multiple Sclerosis (MS)
Translational Candidate (as written by the applicant)	Next generation bispecific CD19 and CD20 directed allogeneic CAR-T
Area of Impact (as written by the applicant)	Progressive Multiple Sclerosis (MS)
Mechanism of Action (as written by the applicant)	The proposed immune therapy consists of allogeneic EBV T cells that have been genetically modified ex vivo to express a CAR that targets CD19 and CD20, which are present on the cell surface of normal, MS CD19+ B and MS CD20+ T cells. Cytolytic function is accomplished through HLA-independent recognition of the anti-CD19/CD20 dual CAR.
Unmet Medical Need (as written by the applicant)	Recent studies have shown a substantial proportion of progressive MS patients are untreated. Most patients continue to have disability progression. There is a need for disease-modifying therapies with greater effectiveness, followed by improved safety and tolerability. Availability of an allogeneic cell therapy would support 'off the shelf' use, unlike autologous cellular therapies that require a lag of several weeks for preparation of therapy before being available for patient use.
Project Objective (as written by the applicant)	Pre-IND FDA Meeting
Major Proposed Activities (as written by the applicant)	• Develop GMP-compatible process towards transfer and production of clinical-scale lot • Complete nonclinical pharmacology studies with representative, research-grade material generated from GMP-compatible process • Complete nonclinical toxicology studies with representative material generated from GMP-compatible process • Develop and validate key biomarkers assays supporting proof-of-mechanisms, PK/PD and immunogenicity • Develop and Draft Phase 1 clinical strategy study design • Conduct pre-IND meeting with the FDA
Statement of Benefit to California (as written by the applicant)	As a California org, we will employ Californians including in R&D and manufacturing, and build expertise and grow the innovation ecosystem. The product has the potential to reduce disease progression of Californians impacted by the disease. Reducing logistical challenges can reduce resource needs for California health systems. The product has the potential to broaden access to community settings, reducing costs while enabling historically undeserved Californian patients to access treatment.
Funds Requested	$3,991,879
GWG Recommendation	***(1-84): Not recommended for funding***
Process Vote	*All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG."* *Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."*

Scoring Data

Final Score: 83

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

Mean	81
Median	83
Standard Deviation	4
Highest	85
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	2
(1-84): Not recommended for funding	13

Key Questions and Comments

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 11 **No:** 2	• Progressive multiple sclerosis (MS) is a debilitating chronic disease with a poor prognosis. Most therapeutic options are available and efficacious only for relapse-remitting forms of MS, not for progressive (degenerative) forms. Therefore, progressive MS, especially secondary progressive MS, represents an unmet medical need. • The proposed drug product is an allogeneic CAR-T immunotherapy based on Epstein-Barr virus (EBV; recently approved) T cells for treatment of progressive multiple sclerosis (MS). This product is likely to impact an unmet medical need. • The project is developing an allogeneic chimeric antigen receptor therapy (CAR-T) therapy that is being used against progressive MS, which is an unmet need. As such finding a treatment for this would be a significant advance given the limited therapeutics available currently. Nevertheless, a key question is whether this therapy could offer more benefits than a monoclonal antibody approach targeting the relevant immune population, as has been tried previously with ocrelizumab and CD20 positive cells. The development of allogeneic CAR-T offers some advantages, but also is not without major challenges in terms of the host response to the therapy and cost. • The proposed therapy is not exactly "off the shelf" because partial HLA-matching is required for its manufacture. A big emphasis was placed on all the advantages of allogeneic off-the-shelf cell therapy products compared to autologous approaches. But the risk of Graft-versus-Host Disease (GVHD) remains real. In this respect, the study to which the applicant in proposal reports 3/16 cases of GVHD (~19%). • The proposed dual targeting CAR-T cells should provide additional benefit compared to current products in development. However it is unclear whether proposed indication is appropriate. • The advantage over autologous CAR-T is unclear, as MS patients could wait one month or so for cell product manufacturing, and their T-cells are not as severely affected as in patients with hematological malignancies.
GWG Votes	**Is the rationale sound?**

Yes: 8 **No:** 5	• There is potentially encouraging initial data with autologous dual directed CAR-T cells.
	• The proposed drug product, will utilize low-alloreactive EBV T cells genetically modified to express dual CD19/CD20 CAR to target CD19/CD20+ B cells and a subset of pathogenic CD20+ T cells, which have been shown to contribute to the pathogenesis of progressive MS. This approach rooted in the available clinical data provides a strong rationale for the project.
	• Although there is considerable evidence for B and T cell involvement in the pathogenesis of MS, this is less clear cut for progressive forms of the disease which may have more of an axonal neurodegenerative basis relating to myelin loss NOT inflammation. There may also be an important role for microglia. As such a number of questions arise:
	  ○ It is unclear why this treatment is being tried in progressive MS rather than relapsing-remitting MS.
	  ○ It is uncertain if this treatment is better than monoclonal Ab approaches.
	  ○ It is unclear how many different lines can and need to be made using this approach to treat all patient.
	  ○ It is not clear if patients need to be given other therapies with this CAR-T treatment such as steroids etc.
	  ○ There is a question of whether this therapy needs to get into the CNS to have maximal efficacy, and if so, whether this has been demonstrated. Despite these criticisms, there is a clear logic to what the applicant is trying to do.
	• It is unclear why the applicant has chosen this scientific rationale (B-cell depletion) for their approach. The applicant appears to assume that the pathogenesis of secondary progressive MS (SPMS) is purely or mostly autoimmune (production of auto-antibody by B-cells). However, it is uncertain whether this is the current consensus in the field. It is more of less clear for relapsing-remitting (RR) form of MS, where B-cell depleting therapy has demonstrated efficacy.
	• In the previous development, the applicant thought that EBV may play a role in the pathogenesis of progressive forms of MS, but their product failed in the 2nd phase (the primary endpoint was not met). The applicant does not discuss it in the project description. But it looks like SPMS may have multifactorial pathogenesis, but it is not inflammatory and the therapeutic value of B-cell depletion remains unclear.
	• Better animal model work needed.

GWG Votes	**Is the project well planned and designed?**
Yes: 7 **No:** 6	• The project is well-planned. The applicant has a very good understanding of regulatory requirements since they have approved product in EU and Biologics License Application (BLA) submitted in the US. • The project includes all activities needed for the planned pre-IND meeting with the FDA. • The project is logical given what they are hoping to do, although as stated above there are some questions around the rationale. The absence of any *in vivo* animal work is justified given no useful models of MS exist in which this therapy could be tried. It may also benefit from a clearer position on what the first in human trial might look like using this approach. Despite these criticisms though, the project is generally well planned and designed. • Pre-clinical proof-of-concept (POC) studies are not generally conducted to confirm dosing regimen and dose rationale as dosing data are not translational. • Pilot safety studies are not generally conducted for a pre-IND; proposed studies could be conducted following agreement of protocols by FDA. • The plan exceeds activities necessary to file a pre-IND.
GWG Votes	**Is the project feasible?**
Yes: 13 **No:** 0	• The project looks feasible. The team is qualified to perform the work. • The project should be feasible. • The proposed milestones are logical and are likely to be achieved within the proposed timeline.

	• The proposal is clear in what it is proposing to do. In terms of specific milestones, there are some risks with Milestone 2, namely the uncertainty of obtaining sufficient cells from the Cerebrospinal Fluid (CSF) of MS patients, which the applicants address. And in addition, it is not clear why Milestone 4 is needed or what biomarker is being developed and for what purpose, given the therapy is targeting specific populations of immune cells that could be assessed using well established methodologies currently available. Overall the project seems feasible.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13 **No:** 0	• The plan addresses but is non-specific. • This is well presented especially given it is developing an "off the shelf" allogeneic cell therapy for people with MS which would allow it to be given away from specialist centers. Although exactly how this would be carried forward into any trial is less obvious. • MS is a debilitating disease that affects people across all races, ethnicities and genders. The MS population in both urban inner cities and in remote rural communities faces significant challenges in accessing novel treatments such as CAR T cell therapies. This is particularly relevant to autologous therapies that require lengthy preparation of patient-specific reagents by highly skilled personnel in major medical centers.

Application #	TRAN3-17055
Title (as written by the applicant)	Synthetic cells for immune cell engineering and immunotherapy
Translational Candidate (as written by the applicant)	Biomaterial-based synthetic cells for enhancing CAR-T cell expansion (stemness and killing capability) for therapy of diseases such as cancer and HIV
Area of Impact (as written by the applicant)	This biomaterial-based synthetic cells will address the needs for more effective cell manufacturing system for CAR-T cells and other cells for therapy
Mechanism of Action (as written by the applicant)	The synthetic cells have superior effects on CAR-T cell activation and expansion, including an increase in T memory stem cells, higher transduction efficiency of CAR into T cells, and robust tumor-killing capability ex vivo and in vivo in comparison to the benchmark for clinical use. This product will significantly improve the quality of manufactured CAR-T cells for more effective therapy of cancer and HIV.
Unmet Medical Need (as written by the applicant)	Cancer and HIV remain leading causes of death in the United States and worldwide. Chimeric antigen receptor (CAR)-T cell therapies have shown success in treating blood cancers and treating HIV by reactivating and targeting the latent HIV reservoir. However, several issues persist, including the lack of efficacy and long-lasting immunity against cancer or HIV. This project addresses the urgent need to develop more effective CAR-T cell expansion techniques.
Project Objective (as written by the applicant)	Finish pre-IDE and get ready for GMP manufacturing
Major Proposed Activities (as written by the applicant)	• Achieve Scalable Production and Comprehensive Characterization of Synthetic Cells • Determine the Activation, Expansion, Stemness Enhancement, and Tumor-Killing (or HIV killing) Efficiency of CAR-T Cells Ex vivo • Demonstrate the Therapeutic Potential of Synthetic Cells-Activated CAR-T Cells in Humanized Xenograft Mouse Model in vivo • Implement Design Control to Ensure the Consistency and Robustness in the Production of Synthetic Cells and GMP-Compliance • Perform Comprehensive Safety Studies of Synthetic Cells for Human T Cell Activation and Expansion • Determine the Regulatory & Clinical Strategy and Prepare the Investigational Device Exemption (IDE) submission
Statement of Benefit to California (as written by the applicant)	Cancer and HIV are leading causes of death in California and beyond. Synthetic cells can significantly enhance CAR-T therapies for treating cancer to improve remission rates, reduce relapse, lower healthcare costs and ease system burdens. In HIV treatment, advanced CAR-T therapies might target latent reservoirs, potentially offering a cure and reducing dependence on lifelong treatment. Additionally, these advancements could drive economic growth and bolster biotech in California.
Funds Requested	$2,810,619
GWG Recommendation	***(1-84): Not recommended for funding***
Process Vote	*All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG."* *Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."*

Scoring Data

Final Score: 80

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

Mean	79
Median	80
Standard Deviation	4
Highest	85
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	1
(1-84): Not recommended for funding	14

Key Questions and Comments

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 9 **No:** 3	• The proposed product would improve CAR-T cell manufacturing and potency. This would improve the use of CAR-T therapies to treat diseases including cancer and AIDS. • The product would improve manufacturing of CAR-T cells by improving CAR transduction efficiency and activity against target cell types. • By improving CAR-T potency, the product would improve the value proposition of engineered immunotherapies, especially for cancer patients, and may extend the use of CAR-T cells to treat other diseases. • The project offers the potential to improve the manufacture of CAR-T cells by promoting the maintenance of a more potent phenotype during manufacture. • CAR-T therapy currently is quite expensive therapy but has been adopted as standard of care in many countries. The development of products that could either enhance the efficacy of CAR-T or decrease the cost to manufacture, will further catalyze the development and expansion of clinical cellular immune-oncology therapeutics. • Development of products that could create CAR-T cells that can have greater expansion, enhanced T cells stemness, and better cancer killing, could lead to better long-term outcomes. • Multiple products that can be used during the GMP manufacture process to develop activated T cells already exist specifically for CAR-T cell development. This device could lead to improved manufacturing opportunities for therapeutic products. The applicant specifically reviewed that, currently, CAR-T therapy for solid tumor malignancy remains underdeveloped, and they believe their product may enhance therapeutic products that can target these malignancies. • Improvement over the current state of art (e.g. Dynabeads) could reduce costs and improve therapeutic outcomes. • The pathway to translation after completion of this project is unclear (e.g. licensing, startup company). • There is some concern about the lack of clear advantages over soluble activation media (e.g., Transact).
GWG Votes	**Is the rationale sound?**

Yes: 11 **No:** 1	• The premise that activating beads that mimic the mechanical properties and size of antigen presenting cells is logical. • The team has presented and published a very impressive set of preliminary data showing that their "synthetic cells" improve CAR transduction and CAR-T activity in vitro and in vivo. • Benchmarking to existing bead technologies is strong. • The use of multiple cancer models and targets is a strength as to the biological significance of the project. • The biological data offer strong support for development of the project to improve CAR-T manufacturing and patient outcomes. • There is no data supporting scalable manufacturing of the product. Development of that at this stage of translation will be crucial to realize the biological promise of the synthetic cells. • Overall, the rationale is sound and there is good preliminary data to support further development of the synthetic cells. • The proposed project is well-designed and outlined. The applicant already developed the alginate synthetic cell and outlined the potential benefits of utilizing these during manufacture. There are studies compared to the well-established Dyna bead which incorporates the same activation antibodies but is more rigid and has less Viscoelasticity properties than their product in development. The studies are designed to confirm the potential efficacy of their product, and, notably, they identify that the manufacturing costs should be significantly reduced compared to alternatives currently in place. • The body of available data support the premise. The investigators indicate that they have developed a centrifugation process that can separate the synthetic cells from the manufactured target cells, with very high removal rate with low-speed centrifugation. Given the fact that the alginate monomers are estimated at 7 to 9 µm in size, it would be critical to also understand that the recovery of the cellular product is maintained at high efficiency. • The data provided within the translational grant support further studies to develop the device for enhancing CAR-T manufacture.
GWG Votes	**Is the project well planned and designed?**
Yes: 7 **No:** 5	• This is a well-designed project which combines expertise that covers the fabrication of the synthetic cells and their application. • The program appears well constructed and will meet quality control on the manufactured products. • Evaluation of the biological potency of the synthetic cells is strong. The goal of demonstrating functional equivalency to Dynabeads is appropriate for a pre-submission meeting. • Identifying and controlling critical process parameters as they relate to critical quality attributes during scalable manufacturing are not sufficiently considered as part of the activity plan. • The overall focus on scale up, design control, safety assessment, and regulatory considerations is appropriate. • Safety considerations are strong. • Evaluation in multiple donors, cell types, in vitro and in vivo models, and indications is a strength of the project. • The investigators indicate that at the end of the grant, they would have the necessary data to allow a pre-IDE meeting with the FDA. They have already initiated the pathway with the director of FDA affairs at the host institution to prepare the documents that would lead to INTERACT and pre-IDE submissions. The investigators have prior experience. • The current program does seem well-designed and developed with clear milestones. The 24-month timeline may be optimistic.

	• The selection of the constructs for testing should be considered more carefully. The selected HIV targeting sequences for CAR production would be unlikely to target latently infected cells. • Lack of benchmarking to liquid activation media is a weakness. • While separation of the beads is considered and will be developed, an assay to quantify residual beads will likely be necessary as part of regulatory approval. • The investigators don't address the ultimate success of the product. The limited manufacturing scale using the team's current technology poses the biggest concern with translation. The team presents some high-level ideas (e.g. scaling out) but does not adequately consider critical process parameters and their effect on product critical quality attributes during this scale-out. For example, heterogeneity may increase, and failure rates may increase.
GWG Votes	**Is the project feasible?**
Yes: 9 **No:** 3	• The timeline is realistic. • Milestones are appropriate and quantitative. • The team is outstanding with expertise across various aspects of synthetic cell manufacturing and evaluation. • All necessary resources are available at the applicant institution. • The team recognizes potential challenges and presents appropriate contingency plans. • Given the team's expertise, the goal of achieving GMP compliant manufacture is feasible. • The milestones are well outlined. There are 6 individual milestones for the development of the product, for assessing the efficacy of the T-cell and CAR-T products manufactured using the alginate beads, as well as a series of safety studies. The 24-month window seems optimistic to achieve the appropriate studies, develop and validate the chemistry, manufacturing and controls within 100% GMP compliance and to perform the comparative T-cell functional studies. • The staff and team have significant experience and represent multiple disciplines including bioengineering, immunotherapy, genomics and CAR-T therapy. They have the experience to perform this project and experience in the development of the alginate synthetic cells already. • The team has access to the necessary resources that would lead to successful performance of the proposed activities. • Appropriate consideration to the removal of the synthetic cells from the final DP has not been fully considered. The proposal does not address the nature, or efficiency of this removal step. • The presented timelines seem overly optimistic. • The investigators outline a series of risk mitigation strategies. They will need to assure that there is batch to batch consistency that could lead to a product that can be distributed. They are aware that there can be variability in the cell performance. They did not necessarily discuss that individual patients with cancer can have quantitative defects in the number of lymphocytes collected for manufacture as well as qualitative defects such as exhaustion from prior therapy. Most of their studies have been performed on volunteer cells but not volunteers that were treated with chemotherapy. They indicate that they have financial resources from multiple institutional sources to assist in the project development.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12 **No:** 0	• The project does an excellent job in using tumors and donor cells from diverse sets of individuals. • All groups of the California population are impacted by diseases for which cellular immunotherapy is a potential treatment. • Costs of cellular immunotherapies represent a barrier to underserved communities receiving these treatments. Technologies that reduce costs could make these treatments more equitable.

	• The investigators' effort at community engagement is to emphasize the willingness to encourage the recruitment of trainees and investigators from diverse backgrounds into the research arena. For the development of a device, it does not necessarily demand input from populations that could benefit, who are the patients who are receiving the T-cell therapies. Their approach to health equity engagement by trying to enhance diverse populations into the research effort, is acceptable for this effort. • The development of a device that can enhance the development of T-cell therapy and CAR-T therapy for all individuals will be beneficial if their product could lead to more efficiency and manufacture and lower the cost of CAR-T. This would increase the likelihood that at risk populations would have access to T-cell immunotherapies. There are publications that clearly indicate that once a patient, despite their race or ethnicity, is referred to an academic center, that their likelihood of receiving a therapy is equivalent to other populations. However, there remains an issue regarding the likelihood that a minority population would be referred, and that may be impacted by the cost of therapy. • The team plans to engage community groups/patient populations. The plan is a little vague and its impact unclear. • The investigators attempt to address synthetic cell development when challenged with cells from disparate HLA types, different sex origins as well as different racial and ethnic backgrounds. They seek a broad pool of donors to assess whether CAR-T cells can be successfully generated after exposure to their product. Again, unless they are addressing the development of universal, allogeneic, off-the-shelf CAR-T product, it would have been strengthened if they could have identified peripheral blood mononuclear cells collected from patients with previously treated cancer. These could include patients in remission for instance, status post adjuvant therapy for stage III breast cancer or patients in active treatment.

Application #	**TRAN1-17022**
Title (as written by the applicant)	CD19-CAR NK cells Secreting an anti-NKG2D–anti-CD22 Bispecific Antibody for the treatment of relapsed or refractory B Cell Malignancies
Translational Candidate (as written by the applicant)	CD19-CAR NK cells secreting a bispecific antibody
Area of Impact (as written by the applicant)	Using a single construct we engineer NK cells (or other cell types) to produce two “living agents” i.e., a CAR and a secreted bispecific antibody.
Mechanism of Action (as written by the applicant)	Our CD19/CD22 dual targeting product is the “off-the-shelf” sIL15.BsAb.CD19-CAR natural killer (NK) cells, which are derived from umbilical cord (UCB) naïve NK cells that are engineered to (1) target CD19 via a chimeric antigen receptor (CAR), (2) express onboard soluble (s) IL-15, as well as (3) secrete anti-NKG2D-anti-CD22 bispecific antibody (BsAb).
Unmet Medical Need (as written by the applicant)	More than 50% of patients treated with CD19 CAR T cells may relapse with CD19 negative escape. A solution is the co-targeting of other B-lineage antigen CD22. The unmet barriers in CAR-T therapies are cytokine release syndrome, neurotoxicity, the waiting period for manufacturing, and high costs. Our product is “off-the-shelf” sIL15.BsAb.CD19-CAR NK cells, which are derived from UCB naïve NK cells that are engineered to (1) target CD19 via a CAR, (2) express IL-15, as well as (3) secrete anti-NKG2D-anti-CD22 BsAb.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Manufacture ≥ 3 lots of sIL15.BsAb.CD19-CAR NK cells from umbilical cord Naïve NK cells • PK and PD of sIL15.BsAb.CD19-CAR NK cells • Perform pilot safety studies of sIL15.BsAb.CD19-CAR NK cells • Optimize treatment schedule of sIL15.BsAb.CD19-CAR NK cells • Confirm the efficacy of sIL15.BsAb.CD19-CAR NK cells under optimized and safe conditions • Pre-IND preparation and submission and Manuscript preparation for publication
Statement of Benefit to California (as written by the applicant)	Recent trends in CA indicate stable or a slight increase of yearly incidence rates of non-Hodgkin’s lymphoma across most populations. Regarding American Indian/Alaska Native populations, there is a concerning increase in incidence rates. Research indicates a disproportionate burden of cancer among lesbian women. Our product is designed as an "off-the-shelf" cell therapy solution, readily available and suitable for any patient, irrespective of their race, age, or socioeconomic background.
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	79
Median	80
Standard Deviation	3
Highest	80
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

Key Questions and Comments

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 6 **No:** 7	• The product is designed to target non-responsive B cell malignancies. • The proposed program does have potential to reduce constraints in treatments, including observed resistance from current treatments for B cell malignancies. The research also notes the potential to target leukemia stem cells expressing CD19. • The product would increase the chances of having a therapeutic that significantly improves current patient care considering the product expresses soluble IL-15 to overcome immune suppression which should enable persistence in the patient. • There is a practical value this program proposes, particularly with regard to the source of the starting materials. The proposal is for an off-the-shelf allogeneic CAR-NKs derived from readily sourced umbilical cord. • The possibility of an off-the-shelf product is the most attractive component of this product. • The product would apply only to leukemia and lymphoma, though there are cases of relapse in these diseases that could benefit from this approach. • Targeting CD19 and CD22 has already been attempted, so the impact on the field may be low. • This approach has previously been tried by other investigators. The potential impact of this science seems quite limited. • The value proposition includes proposed cost savings but this argument was weak. • There are many competing products on the market. The innovation potential of this project is incremental. • Investigators mention the advantages of umbilical cord cells as having greater plasticity and decreased cytokine release syndrome (CRS) and graft-versus-host disease (GvHD) but they could also be weaker effector cells which is concern for cord blood transplant relative to peripheral blood. Little preliminary data is provided to support these points.
GWG Votes	**Is the rationale sound?**
Yes: 11 **No:** 2	• The scientific rationale provided by the proposed project is sound based on the proof of concept data provided and supporting references. The expected product profile is consistent with other allogeneic products currently going through clinical development.

	• The data provided for the current state of the product's development does support the scientific rationale. Included in the supporting elements is early evidence of product manufacturing consistency where functional NK cells were shown following a freeze-thaw cycle via a cytotoxicity in vitro tumor model. • The NKG2D-based BsAb allows NKG2D(+) cytolytic immune cells such as NK, CD8+ T, NKT, and γδ T cells to migrate to and effectively eradicate CD22+ tumor cells. • Overall, the data supports further development of the product into translational activities. • Yes, the concept has also been tested clinically with cells only or antibodies only. • Other than being an off-the-shelf product, it's unclear if this will provide a substantial benefit to patients that is more effective than other approaches. • Innovative. Scant preliminary data.
GWG Votes	**Is the project well planned and designed?**
Yes: 9 **No:** 4	• All of the the proposed activities are necessary to advance the project into clinical development. And considering the expected ~8 months to complete the manufacturing activities outlined in milestone #1, the project's timeline demonstrates strategies that are commensurate with CIRM's mission. • Innovative two in one approach: "off the shelf" and ability to engage other cytolytic cells in addition to T cells. There is a company track record in California with NK cells and clinical trials including one for a different indication using a different approach. • Yes, the pharmacology/toxicity data will be helpful for the pre-IND meeting. It will be important to optimize the dosing plan prior to the pre-IND. • The program's readiness includes activities for generation of feeder cells and their subsequent development to GMP grade, production of master and working cell banks to stably produce the CAR virus with tests for replication competency. The current aims to isolate umbilical cord naïve NK cells and freeze, generate virus particles from the producer cells, transduce NK cells with the CAR virus, and subsequent analytics proposed meet the requirements necessary to support meeting with the agency to advance further into regulatory development space. • The program is constructed well with appropriate elements consistent with the principles of quality by design. • The scope is too broad and ambitious. Unclear if the team will actually be able to succeed in terms of execution. • Workload may be too much for staff listed in application. Limited umbilical cell source - this source is not readily available.
GWG Votes	**Is the project feasible?**
Yes: 9 **No:** 4	• The company has a good track record. • From a manufacturing perspective, the project outcomes are likely to be achieved but with some concern that the activities may take longer than anticipated. The proposed timelines may be slightly aggressive considering the interdependencies of the sequential activities. • Qualifications of the team proposed come across as appropriate for the work expected but the number of staff may be stretched given the number of responsibilities. • Access to the necessary resources to conduct the proposed CMC activities is in place as described. Some staffing resources may be limited to achieve the objectives in the time expected. • Contingencies are already in place for the CMC activities which are dependent on timely supply of materials. As outlined in the application, the team has pre-ordered and maintained a stockpile of critical supplies to cover any potential issues. • Yes, the project is feasible but it's unclear if it's any better than the myriad of strategies out there targeting CD19 and CD22. No head to head comparison data are presented and the applicants only show data with the lead compound in a suppression study. • There were concerns about whether this product can be adequately manufactured from a cord blood unit.

GWG Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
Yes: 11 **No:** 2	• The project upholds principles of diversity, equity, and inclusion (DEI). • To an extent the project plan does address the influence of race, ethnicity, sex and gender diversity. Some internal activities include provisions for cultural sensitivity and DEI training for the project's PI, team members, and other personnel. • It is difficult to directly determine if the program's outcomes would develop a product that serves the unmet medical needs of the diverse California population. The applicant provides some context with regard to 'aims to transcend disparity,' as they note it is created to be effective against B cell malignancies across all sexes and ethnicities. • The applicant has provided context from CAL*Explorer data reveals where minority groups consistently exhibit lower survival rates than Non-Hispanic Whites for the proposed indication. They also note a concerning increase in incidence rates for Native populations. However, it not clear how the perspectives and experience from the populations are expected to be incorporated. • The section regarding health disparities was difficult to follow in terms of what disparities could be addressed by this project. • The application was light on specifics.

Application #	TRAN2-16931
Title (as written by the applicant)	Comparative Analysis of RNA Expression (CARE) to define developmental biomarkers and targets for pediatric malignancies
Translational Candidate (as written by the applicant)	Comparative Analysis of RNA Expression (CARE) assay for pediatric cancer patients
Area of Impact (as written by the applicant)	Children, adolescents and young adults with difficult-to-treat or rare tumors
Mechanism of Action (as written by the applicant)	The CARE assay conducts RNA sequencing of pediatric tumor samples and reports canonical and non-canonical transcripts. The expression of canonical transcripts is quantified as "high" or "not high".
Unmet Medical Need (as written by the applicant)	As of June 2024, there are no FDA-approved RNA sequencing assays specifically designated for pediatric cancer patients. However, there is extensive evidence that RNA sequencing can refine diagnoses and identify treatment targets not apparent from DNA analysis. Therefore, this assay will improve the clinical care of pediatric cancer patients by identifying additional personalized treatment options not apparent through other analyses.
Project Objective (as written by the applicant)	Completion of CLIA validation in a clinical lab
Major Proposed Activities (as written by the applicant)	• Demonstration of analytical accuracy, precision and reproducibility of non-canonical transcript detection • Demonstration of analytical accuracy, precision and reproducibility of canonical transcript detection • Implementation of the computational and regulatory framework to support clinical testing
Statement of Benefit to California (as written by the applicant)	Every year California has nearly 400 pediatric cancer cases that don't respond to standard treatments. These children need new methods to identify effective options to fight their diseases. CARE is a novel diagnostic assay, which could indicate appropriate therapies for these patients, helping pediatric oncologists identify additional treatment options, and providing new hope to kids with difficult-to-treat cancers. This will be the first assay of its kind in California and beyond.
Funds Requested	$1,828,777
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	75
Median	80
Standard Deviation	6
Highest	81
Lowest	65

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

Key Questions and Comments

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 9 **No:** 4	• Yes, there is a small, but real, need for the enhanced diagnosis of rare/refractory pediatric tumors. • This diagnostic would probably result in a national "core" type lab to analyze samples from around the country (or world), and this would be a resource for cancer centers. • As of July 2024, there were no available RNA sequencing assays that can be used to detect canonical and non-canonical transcripts specifically for the diagnoses of difficult-to-treat pediatric cancers that can help to define treatment strategies. This presents a significant unmet medical need. • The intention of the award is to transfer the CARE assay from a genomics laboratory environment to a university pediatric oncology unit to enable patients from all walks of life to have access to tumor diagnosis and treatment options. • The potential for high impact is described through the detection of a gene whose RNA transcripts are detected as "high" in the CARE assay and is being used as a biomarker and companion diagnostic for the detection and diagnostic for neuroblastoma in pediatric patients. • The proposed product is a bioinformatics pipeline to integrate tumor RNA sequencing data into treatment determinations. It is possible that additional information, such as overexpression of certain oncogenes or fusion transcripts, can be useful to determine potential treatment options. • The possibility highlighted, that the diagnostic could enable a cell-based therapy (CAR-T) to be developed that targets the tumor, is a bit of a stretch. It's much more likely that a specific chemotherapeutic would be used in a more directed manner. • No. The applicant proposes that this technology can be useful to identify tumors with antigens for cell therapies, such as CD20- or GD2-targeted CAR-T. However, no data was provided that the pipeline can identify either of these antigens. • This project is potentially impactful.
GWG Votes	**Is the rationale sound?**
Yes: 8 **No:** 5	• Yes, the proposed project is based on the idea that transcriptomic information can provide additional targets that whole genome or exome sequencing may not, including the overexpression of certain oncogenes or immunotherapy targets. • Many childhood/pediatric cancers go undiagnosed because they are derived from flawed stem cell differentiation and are different from adult cancers. The potential to use an RNA sequencing assay that can detect BOTH canonical and non-canonical from gene fusions forms a sound rationale. • There is some data provided that this pipeline has been used in a small clinical study, and less than ten patients were treated according to recommendations from the RNAseq analysis. However, the best responses were progressive or stable disease. • There is no data provided that the CARE pipeline can identify targets for CAR-T cells, including GD2 which is mentioned frequently through the proposal. • There is insufficient data in the application that the CARE pipeline can identify targets for CAR-T cells as proposed.

GWG Votes	Is the project well planned and designed?
Yes: 6 **No:** 7	• The primary aim is to validate the RNA-seq assay and obtain CLIA certification to utilize it in a clinical setting. The applicant has outlined a plan to obtain certification and generate a regulatory framework working closely with FDA. • The potential to achieve the project goal to identify biomarkers of pediatric cancers has been demonstrated through the identification of a gene dysregulated in neuroblastoma. The plan includes utilizing the assay to define characterization of tumors and treatment options. This has already been spearheaded by the team. • Yes, regulatory considerations are discussed. • Yes, the milestones are clear and concrete with defined metrics for success. • Yes, the work is consistent with quality by design principles. External RNA Controls Consortium (ERCC) spike-ins and dilutions of tumor RNA to determine the lower level of detection and necessary RNA inputs are all consistent with developing a quality pipeline. • Yes, timeline is appropriate, and the activities are essential. • Reviewers questioned the absence of a comparison of normal patient tissue versus the planned database. While this would require normal tissue, each tumor is resected with a margin of normal tissue (or at least that is the surgical goal). If this border tissue isn't possible, a normal biopsy could be obtained. This comparison to normal tissue is absolutely critical to identify specific biomarkers.
GWG Votes	**Is the project feasible?**
Yes: 9 **No:** 4	• The team is uniquely qualified for this activity, building upon existing infrastructure. They have the appropriate software engineers, and bioinformatics experts. • Feasibility has been demonstrated with the development of a companion diagnostic biomarker based on data derived from the CARE assay. The potential to identify other possible biomarkers and obtain validation for them is therefore feasible. • Yes, the milestones are clear and achievable - although ambitious. • Yes. The only thing that may be an issue is input of rare tumors into the pipeline in early stages of the process.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12 **No:** 1	• The applicants have several plans in place to ensure that patients who are typically "left behind" with respect to advanced diagnostics are included. CLIA validation means that patients from under-served communities will be included as this laboratory will become the service unit potentially for the whole of California. • There is a plan to work closely with patient advocacy groups to assist with outreach to underserved communities. • The majority of panelists agree that the proposal upholds DEI principles.

Application #	TRAN4-16946
Title (as written by the applicant)	Automation to Standardize and Scale Cell Therapy Delivery
Translational Candidate (as written by the applicant)	A process automation tool designed to standardize and simplify the 'last mile' cell/gene therapy drug dose preparation process.
Area of Impact (as written by the applicant)	A limited set of hospitals are delivering cell and gene therapies (CGTs) to patients today, largely due to the specialized infrastructure and institutional know-how required.
Mechanism of Action (as written by the applicant)	Our process automation tool is a liquid handling automation system that is a combination of innovations in microfluidics, robotics, and materials science. The innovative design will enable standardization and miniaturization of the 'last mile' infrastructure required to deliver CGT drugs to patients. Translation of this product will enable a larger number of hospitals to deliver cell therapies to patients.
Unmet Medical Need (as written by the applicant)	Cell and gene therapy (CGT) biopharma companies and hospitals are struggling to deliver CGTs to patients. Today, these therapies can only be delivered at large academic medical centers given the need for trained staff and specialized equipment; this has significantly limited patient access. Our proposal will advance a product designed to reduce the infrastructure required to deliver a CGT drug into a box, thereby dramatically expanding access to these life-saving therapies.
Project Objective (as written by the applicant)	Product is ready for transfer to manufacturing
Major Proposed Activities (as written by the applicant)	• Optimization of Microfluidic Cell Wash and Resuspension Feature • Hardware and Software Full Integration • Validation studies via pilots with CGT developers and hospitals
Statement of Benefit to California (as written by the applicant)	Access to cell and gene therapies (CGTs) is limited by the specialized hospital infrastructure (personnel and equipment) required for delivery to patients. CGT delivery limited to academic medical centers leads to serious healthcare disparities in care, and thus represents a growing unmet need that will become even more prevalent as the field matures. The proposal will advance a product to enable CGTs to be delivered at any hospital, eventually enabling broader access to CGTs for all Californians.
Funds Requested	$861,592
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	72
Median	80

Standard Deviation	11
Highest	80
Lowest	50
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

Key Questions and Comments

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/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	• Very broad application - this is a product that is missing from the market. • Many cell therapy products require manipulations like thawing, washing and concentrating at the site of administration which is usually a hospital or other clinical setting. The proposed project aims at finishing the development of a machine that can do all of those steps in a controlled way. • The product could be used in both the clinical trials setting as well as after product registration. The fact that the process is programmable is quite attractive as it removes the need for specialized training and removes potential human error or variability from the process. • While controlled GMP manufacturing of cell and gene therapy products exists, it is not available at the site of administration of the CGT product. This machine potentially will make the preparation of the CGT more standardized and uniform.
GWG Votes	**Is the rationale sound?**
Yes: 9 **No:** 3	• There is a need for this type of technology. The instrument is based on a disposable microfluidics card. This technology has been around for quite some time, so the idea of using disposable cards with validated technology like microfluidics is sound and rational. • The rationale is sound, but how this would actually "play out" in the real world is unclear. If this in effect makes each site that uses this system involved in "manufacture" then it isn't a reasonable or viable approach. • The applicant provides a very limited amount of data using a prototype with a number of cell therapy companies. The results show that cell viability, recovery and functionality are as good manual processing but the limited amount of data makes it hard to judge. • There are questions about the origin of the ideas this technology is based on. There is little proof of concept work. There is no information on addressing sterility.
GWG Votes	**Is the project well planned and designed?**
Yes: 8 **No:** 4	• The main aim is to bring the equipment into GMP manufacturing by implementing design controls appropriate for a device. • The applicant has identified the steps they need to take to bring the device into regulatory compliance for use in a clinical setting. • A limited amount of data is presented in the application. • It is a great concept to automate aspects of cell therapy delivery, but there is concern in the proof-of-concept data and plans for use of a contractor for manufacturing the device. Content overall was limited to support the application's premise.
GWG Votes	**Is the project feasible?**
Yes: 10	• Manufacturing details are lacking, subcontractor/collaborator work. • The timelines are quite tight.

No: 2	• The contingency plans are reasonable, but there could be delays which will impact budget and product launch.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12 **No:** 0	• OK; not so relevant for this application. • Given this is a device that will be used in the preparation of cells at the site of patient administration, it's unclear how they would impact DEI.

Application #	TRAN1-16966
Title (as written by the applicant)	Advancing a non-viral high-fidelity KLKB1 gene editing candidate for hereditary angioedema
Translational Candidate (as written by the applicant)	Candidate is non-viral nanoparticle, delivering a very specific gene editing system, for fewer unintended effects, as a durable treatment for hereditary angioedema (HAE)
Area of Impact (as written by the applicant)	Targeted reduction of pre-kallikrein lacks durability and consistency, leaving serious gaps regarding disease outcomes, quality of life, and access
Mechanism of Action (as written by the applicant)	The candidate aims to treat HAE by reducing the production of kallikrein, an enzyme that causes swelling attacks, that can be deadly. The candidate employs a particularly precise gene-editing tool, to target and modify the KLKB1 gene in liver cells, lowering kallikrein levels by stopping production at the source. This permanent gene edit is intended to reduce HAE attack frequency and severity, providing long-term durable relief without the need for continuous medication.
Unmet Medical Need (as written by the applicant)	The proposal and candidate aims to address the unmet medical need for HAE by offering a long-lasting treatment. Unlike current treatments requiring continuous medication, the candidate to be advanced here uses especially high-fidelity precise gene editing with the goal of permanent relief. This approach minimizes attack frequency and severity, improves quality of life, reduces emergency visits, and lowers overall healthcare costs, offering a safer and more effective long-term solution.
Project Objective (as written by the applicant)	Pre-IND success. Ready to start IND-enabling studies.
Major Proposed Activities (as written by the applicant)	• Process Development: Complete bench-scale process development. Demonstrate reproducibility at pilot scale. Refine and optimize production processes. • Tech Transfer, Scale-Up: Transfer process to contract manufacturer. Development runs to ensure reproducibility. Pilot-scale runs to confirm conditions and quality. • Generate Non-GMP Batches: Engineering batches of drug substance and drug product. Validate process at scale. Generate reference material for analytical and stability. • Development and Qualification of Release Methods: Transfer internal assays to contract manufacturer. Verify compendial methods. Qualify product-specific release methods. • Stability Studies: Conduct stability studies at various conditions (long-term, accelerated, and stressed conditions). Monitor product quality over time. • Pharmacology and Safety Studies: Rodent dose range-finding and efficacy studies. POC durability and biodistribution. Pilot safety studies.
Statement of Benefit to California (as written by the applicant)	HAE imposes a burden on California's healthcare system due to its unpredictable and severe attacks. By developing a safe and durable gene editing therapy, we aim to create a functional cure to improve outcomes and QoL for patients, including those in California. We will provide economic benefits to California by advancing next-generation genetic medicine, forging

	collaborative relationships with top investigators at California universities, and advancing innovation in California.
Funds Requested	$4,322,830
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: 79

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

Mean	77
Median	79
Standard Deviation	7
Highest	85
Lowest	60
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	2
(1-84): Not recommended for funding	11

Key Questions and Comments

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 5 **No:** 6	• There is a potential to improve patient care if the proposed technology can cure some patients, have fewer side effects, and compete in terms of cost with available therapies. • The product targets liver KLKB1 gene to reduce kallikrein levels and ameliorate attacks of hereditary angioedema. This has the potential to prevent attacks and provide long-lasting remission. A potential strength is the possibility that a single dose of the product might induce prolonged biological and clinical effect; although, this remains to be demonstrated. • The unmet medical need in HAE is not clear from the application. There are therapeutic options available for these patients - approved KLKB1 inhibitors, and antisense oligonucleotide and gene editing technology in development (with promising results). Seems like none of them are perfect, and they are not curative. • It was unclear from the application how this is an unmet need. • The proposal addresses a very rare disease. • The competition from KLKB1 gene editing technology could be underestimated. The competitor is in the pivotal (registration) phase of the trial with excellent results. Also, as of today there are no reports on off-target editing issues in trial. So, even though the expectation is to have fewer off-target editing issues with proposed technology compared to conventional Cas9, the clinical impact of it at this point is just a

	speculation. We have to wait for long-term follow-up studies to see all potential off-target gene editing issues in patients. • Limitations include that many HAE patients might experience infrequent attacks that can be managed by "on-demand" therapies. Second, there are already similar gene-editing efforts (e.g., Cas9) which have already produced significant reduction in kallikrein levels and HAE attacks; although there are some potential advantages of the new product over these existing approaches, direct comparisons are not available. Differences in the rate of "off-target" effects might require long follow-up to determine their clinical significance. • The program does have a strong value proposition but it may be up against significant competition with current standards of care. • It was unclear from the application how significant the unmet need is, as several approved therapies were mentioned as well as other effective approaches in clinical development. • While the therapy could reduce the number of treatments currently needed, it was not clear how much better this would be than the Cas9 approach that is in Phase 3 of clinical development.
GWG Votes	**Is the rationale sound?**
Yes: 11 **No:** 0	• The scientific rationale is sound. Preliminary data support the rationale. • The approach is based on sound rationale and has been demonstrated clinically. • The high-fidelity platform delivered through nanoparticles holds promise to induce long-lasting reduction of KLKB1/kallikrein and, accordingly, durable control of HAE attacks. The platform has high accuracy against its target, thus minimizing off-target, potentially genotoxic effects. Adequate preclinical studies and supporting data are presented. • HAE has a defined genetic basis, resulting in increased kallikrein levels and vasodilation driving soft-tissue swelling/angioedema attacks. Therefore, the product (gene-editing of the liver KLKB1) targets the disease pathophysiology. • Extra-liver expression of KLKB1 exists (albeit at lower levels) especially in gonadal tissue, therefore safety studies, already described in the proposal, are required to address any potential genetic/clinical effects in these tissues. • The claims that this approach is safer than a Cas9 approach were not strongly supported by the information provided. • There is a rival product in clinical trials.
GWG Votes	**Is the project well planned and designed?**
Yes: 10 **No:** 1	• The project is well planned. • The applicant is incorporating feedback from an INTERACT meeting, and the nonclinical studies are appropriately designed. • The proposal is well-written/structured and includes preclinical and clinical steps such as: manufacturing, dose-ranging/refining, release studies, several safety studies in humanized mouse models. The regulatory and clinical path is also clearly outlined, including an adaptive Phase 1/2 clinical trial in human patients.
GWG Votes	**Is the project feasible?**
Yes: 10 **No:** 1	• The timeline and milestones look feasible. • Most of the work will be outsourced (to contract manufacturer for manufacturing, regulatory consultants). • A number of contract organizations will be engaged across different tasks, in particular the drug product process will be transferred to a contract manufacturer for further development and scale-up. • The team has previous experience using/implementing the proposed gene-editing platform. They have a large number of specialized staff/researchers which will undertake parts of the project. • Yes, high quality team organization. Some relevant risks were identified with contingency plans. • Possible risks and appropriate mitigation strategies are presented.

GWG Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
Yes: 11 **No:** 0	• Specific activities were identified for enhancing participant engagement and improving the trial design. • Several topics/aspects related to DEI are presented in the proposal. It is emphasized that HAE impacts people of all races and sexes equally. The named center at a large public California university manages a very diverse patient population. • The group notes the underrepresentation of minorities observed in existing HAE trials; they seek to develop a therapeutic that will demonstrate equity in access and availability to patients, and in education to key opinion leaders and physicians. During the product development process, the applicant will undertake an effort to hit enrollment close to the demographic split for the disease. • Health equity community engagement activities are also outlined. • Future efforts to enhance DEI principles are also discussed, in particular by (a) conducting longitudinal studies on the diverse experiences of HAE patients in clinical trials; (b) expanding patient engagement initiatives to include more diverse subpopulations and ensuring a comprehensive understanding of HAE across different demographic groups.

Application #	TRAN1-16950
Title (as written by the applicant)	Autologous anti-PSMA CAR-T cell controllable by focused ultrasound
Translational Candidate (as written by the applicant)	Autologous anti-PSMA CAR-T cells controllable by focused ultrasound
Area of Impact (as written by the applicant)	Localized prostate cancer treatment, addressing low efficacy and significant side effects of current therapies with non-invasive CAR-T cells.
Mechanism of Action (as written by the applicant)	The proposed CAR-T cells aim to treat localized prostate cancer by using focused ultrasound to precisely activate CAR-T cells at the tumor site. This targeted approach enhances tumor-killing efficiency and minimizes off-tumor toxicity, addressing the need for safer, more effective treatments. It reduces systemic side effects associated with current therapies like surgery and radiation, potentially improving patient outcomes and quality of life.
Unmet Medical Need (as written by the applicant)	The proposed CAR-T cells address an unmet medical need for safer and more effective localized prostate cancer treatment. Current therapies, such as radical prostatectomy and radiation, often cause significant side effects, impacting quality of life. Traditional CAR-T therapies face challenges with low efficacy and off-tumor toxicity. Our approach uses focused ultrasound to activate CAR-T cells at the tumor site, minimizing off-tumor effects and improving safety and efficacy.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Produce GMP-like grade lentivirus, generate CAR-T cells, and conduct in vitro and in vivo studies to assess their efficacy, cytotoxicity, and safety. • Complete studies on the efficacy and distribution of the CAR-T cells in xenograft and PDX tumor models to demonstrate its therapeutic potential. • Scale up GMP-grade CAR-T cell production, calibrate the clinical focused ultrasound system, and compile a comprehensive pre-IND submission package for an FDA meeting
Statement of Benefit to California (as written by the applicant)	Prostate cancer is one of the leading cancers affecting males in America. Approximately 268,490 new cases were reported in America, with 26,890 new cases in California. Secondary to lung cancer, prostate cancer is the leading cause of cancer related deaths, which exceeded 34,400 male lives. Racial and ethnic disparities exist as African-American males between 40 to 64 years of age are more likely to be diagnosed and are twice as likely to die of prostate cancer than Caucasian/White males.
Funds Requested	$5,492,879
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	78
Median	78
Standard Deviation	8
Highest	90
Lowest	65
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	4
(1-84): Not recommended for funding	10

Key Questions and Comments

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 9 **No:** 2	• The proposed product could improve the current options for preserving urogenital function in prostate cancer patients. • In this revised submission, the applicant has further supported the likelihood of an impact to an unmet medical need with data showing relatively minimized off-tumor toxicity of standard PSMA CAR-T cells. • The proposed CAR-T uses a heat shock promoter (HSP) and therefore can be activated using heat. Focused ultrasound is expected to increase the heat at the site of irradiation/ablation. • The proposed product would increase the likelihood of successfully developing a cell and gene therapy technology based on both advances (the therapeutic approach and the ultrasound ablation device). The project should broaden the community's experience and regulatory understanding. • The applicant seeks to make newer types of inducible PSMA targeting CAR-T cells for prostate cancer, increasing the likelihood of successfully developing a therapy. • Yes, the product may accelerate a genetically engineered cell therapy and allow for larger doses of cells to be administered to patients. Local activity of the cell therapy is limited by focused ultrasound exposure to tumor regions. • Yes. The proposed product is likely to impact advanced prostate cancer. • The practical value proposition for patients comes from the applicant's approach: focused ultrasound to confine cell activation within deep tissue tumor sites while achieving precision with the ultrasound device. It is easy to understand why the therapy's impact could extend to other solid tumors. • Yes, the product may be potentially impactful for patients. PSMA CAR-T cells have previously shown activity in prostate cancer but there is potential toxicity associated with off-target recognition. • This proposal will use focal ultrasound on the implanted tumors or inside prostate cancer following local injection of PSMA targeting CAR-T, which can only be activated following focused ultrasound-mediated hyperthermia at a specific temperature. • The proposed product doesn't really offer a sufficient, impactful, and practical value proposition. The process will be limited to local tumors and will not affect distal metastasis. Prostate cancer is notorious for developing metastasis. • During this TRAN review cycle, the FDA approved a pivotal trial using Procept Biorobotics for assisted aquablation therapy with potential for approval in 2026. This development may impact the significance of the proposed project.

GWG Votes	Is the rationale sound?
Yes: 6 **No:** 5	• Previous experience with focused ultrasound CAR-T cells with a different target and initial in vitro and in vivo data with focused ultrasound PSMA CAR-T cells support rationale. • Based on the demonstrated in vitro and in vivo efficacy and the in vivo safety of the CAR-T cells, the proposed project with the ultrasound ablation system is supported by a sound scientific rationale. • The in vitro and in vivo data supports the CAR-T's efficacy and safety and the data from the focused ultrasound for small animal's data supports the device-based delivery approach. • Yes, the product will express PSMA-targeted CAR when induced by ultrasound. The CAR transgene is expressed under the control of a protein promoter. When local temperatures rise to a specific temperature, the CAR is expressed and the T-cells can exert lytic activity. However, when the cells are outside of the ultrasound region, the CAR expression diminishes to decrease off-target toxicities. • The rationale is supported by the body of available data. • Yes, the data is strong and supports that this product will have efficacy when controlled by ultrasound. • The overall body of data does support advancing development of the product further into clinical settings. • The rationale is sound but complicated - with two different technologies to be synchronized. Moreover, PI is not considering treating metastatic prostate cancers. • The rationale is not supported by the body of available data. Most of the preliminary data are from cells that are not related to the proposed project. • An important control is missing from most of the preliminary data. The PI has not shown the effect of focused ultrasound-mediated hyperthermia in tumors that are injected with standard PSMA CAR-T cells. The effect of focused ultrasound-mediated hyperthermia is not canceled out. • It is possible to develop this product, but whether it will be effective remains to be determined. • There are insufficient relevant preliminary data to support this project.
GWG Votes	**Is the project well planned and designed?**
Yes: 4 **No:** 7	• The project includes the steps consistent for a program with a delivery device to meet the objectives for a pre-IND submission and subsequent IND application. • The applicant has submitted communications with the FDA (INTERACT) and plans for future communications, including pre-IND meeting. • Based on the program's scientific design and the current results to date for in vivo efficacy including comparable demonstration of a portable system, the program is consistent with the principles of quality by design. • Yes, the design principles are well-constructed. • Essential activities, which include generation of GMP grade cells and vector, conduct engineering runs and qualification runs, do show an appropriate strategy which is consistent with CIRM's mission. • Production of GMP material exceeds readiness for a pre-IND meeting. • Pilot safety studies are generally not conducted for this type of product, as dose is not translatable to the clinic. • No discussion of the impact of different routes of administration between preclinical and intended clinical route is provided, nor justification for proposed repeat dosing described in the target product profile. • No discussion is provided regarding the proposed clinical route of administration, i.e., experience to inform dose. • The timing of patient selection criteria and study in patients is unclear. • The proposed method for calibration of the clinical ultrasound system should be agreed upon at the pre-IND prior to conducting the study.

	• The project needs to be approved by the FDA as a new IND, provided the ultrasound system is approved.
GWG Votes	**Is the project feasible?**
Yes: 8 **No:** 3	• The proposed timelines seem appropriate for a product that includes a device. The project outcomes, overall, come across as having generally low risk. • The proposed milestones and the expected project outcome are likely to be achieved within the proposed timeline. • The proposed project can be achieved within the proposed timeline. However, the project will be dependent on the institutional facilities. • The proposed team is appropriately qualified across all functions. They have the expected number of staff to support a project of this design. The applicant team has a diverse set of experiences that will benefit the program and the cell and gene therapy community. • The proposed team is appropriately qualified and staffed. However, it is not clear why the PI is requesting help from a consultant from overseas to go through the US FDA approval process. • Essential activities including generation of GMP grade cells and vector, conduct of engineering runs, and conduct of qualification runs, show an appropriate strategy that is consistent with CIRM's mission. • The applicant has provided clear documentation of (i) their access to the cell therapy facility at a nearby academic medical center, (ii) appropriate support from the industrials partner associated with the device, and (iii) support from qualifying facilities for testing, research, and development. • The team has access to all the necessary resources to conduct the proposed activities. • The team has a viable contingency plan to manage risks and delay.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 11 **No:** 0	• The project plan adequately upholds principles of DEI. The applicant has addressed previous concerns from past reviews and advanced further in their approach. They revised the proposal to include a detailed plan for DEI and an associated partnership with a CIRM Alpha Clinic. • The project's resultant product should provide for the unmet medical needs of the diverse California population. As detailed in their plan for DEI, they plan to conduct safety studies using cells from a diverse cohort. • The detailed plan for DEI includes establishing a Community Advisory Board led by personnel from backgrounds heavily impacted by prostate cancer. In this way, the applicant incorporates experiences from the population that would benefit from this product. • The project plan and design adequately address and account for the influence of race, ethnicity, sex and gender diversity. • A comprehensive DEI plan has been provided.

Application #	TRAN4-17058
Title (as written by the applicant)	hiPSC MPS (organ-on-chip) based drug screening platform for age-associated degenerative diseases.
Translational Candidate (as written by the applicant)	A tool for drug-screens of new therapeutics against co-morbidities of aging that help racially, ethnically, and socioeconomically diverse populations.
Area of Impact (as written by the applicant)	There are no effective treatments for debilitating age-associated diseases and health-span inequalities are not well-addressed.
Mechanism of Action (as written by the applicant)	Our labs have been collaborating on this project for a year and shown that a long list of aging hallmarks can be created and detected in the aging-on-chip organ system. Aging associated dysfunctions are established within days and are partially reversed by drug candidates. Our goal is to turn these exciting new findings into an effective technology tool that will empower rapid screens of drug targets and therapeutic candidates to enhance healthy longevity for diverse demographics.
Unmet Medical Need (as written by the applicant)	Genetics and environmental factors influence the burden of aging-associated diseases, and environmental inequalities are, sadly, expected to worsen with the climate change. However, development of much needed medicine that enhances healthy longevity for all demographics is stalled because there is scarcity of studies on diverse groups and a lack of pre-clinical platforms for understanding human aging, both as a fundamental process, and equitably applied to diverse populations.
Project Objective (as written by the applicant)	Readiness for transfer to manufacturing
Major Proposed Activities (as written by the applicant)	• To define the effects of human diversity on the system and to understand the dynamics induced by human diversity on the read-outs of the device. • To optimize the robustness and effectiveness of the system to accurately detect the aging-caused dysfunctions for diverse demographics. • To optimize the system for robust, effective, accurate, and reproducible longevity drug screens using the samples that represent human diversity. • To optimize the system for the ease of manufacturing and deployment by the end users - biotech and Big Pharma industries. • To transfer the system to the end users. • To work with the end users and the DEI leadership of UC and CIRM to ensure the equitable and just use of the system.
Statement of Benefit to California (as written by the applicant)	Californians, California scientists, California biotech and health industries, and people worldwide will benefit from a paradigm shifting new technology that enables re-creating aging-associated pathologies of complex internal human tissues, within days, performs drug screens for longevity therapeutics that help ethnically and socioeconomically diverse populations, and have sufficient robustness, effectiveness and reproducibility to be shared with commercial partners, empowering new medicine.
Funds Requested	$1,614,000
GWG Recommendation	***(1-84): Not recommended for funding***
Process Vote	*All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG."* *Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."*

Scoring Data

Final Score: 70

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

Mean	69
Median	70
Standard Deviation	7
Highest	82
Lowest	55
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

Key Questions and Comments

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 7 **No:** 6	• The main goal of this proposal is to develop a liver/adipose tissue organ-on-chip system to model aging. Aging, and more importantly healthy aging, is a major clinical challenge. This product is definitely addressing an unmet clinical need. • Yes. Everyone ages and doesn't want to do so. • The resulting organ-on-chip system could be used to identify divergent factors in the serum of old vs. young donors. It could also be used to identify factors that reverse the effects of aging. • The tool may be useful for screening small molecules for their impact upon aging readouts in a high throughput manner. • The applicant strongly emphasizes the importance of ethnicity in aging. Their project will ensure that this aspect is properly considered. • If successful, this project could have an important impact on a diverse group of patients. • It's difficult to understand how the proposed tool will be useful in drug development. • The applicant did not make a strong case that they are developing a tool that could help patients. This appears to be more of an academic research pursuit which might identify new drug targets, rather than a tool for screening drugs. • The key issue is whether the focus on liver/adipose tissue will fulfill the applicant's objective. • It's too early to tell the value of the proposed tool for patients.
GWG Votes	**Is the rationale sound?**
Yes: 4 **No:** 9	• The rationale is somewhat sound. The applicant assumes alterations in the chosen read-outs are reliable surrogates for aging. It isn't a bad assumption, and has a sound rationale, but aging is probably much more complex than presented. Nevertheless, the approach is still useful if it corrects "metabolic syndrome" and not really aging per se. • The concept of a "phenotype" for aging isn't entirely sound. Without such a phenotype, the rationale for this project doesn't make sense. • The application provides a rationale for comparing 'old' and 'young' serum cultured in tissue systems, but there is limited explanation of the expected tool outputs.

	• The preliminary data are impressive in quality and quantity. Human serum from old donors increases the aging phenotype in vitro. However, the difference observed, while statistically significant, seems limited. • There are some data indicating that different phenotypes are observed between 'old' and 'young' serum; however, the biological relevance of this data is unclear. • Aging is a complex process which involves interplay between environment, societal, and innate factors. Modeling such multimodal mechanisms using organ-on-chip seems challenging. • The fundamental premise that the aging phenotype can occur in the timeframe described raises reviewer concern. The phenotype may be an incomplete manifestation of true aging or an epiphenomenon related to the methods used. It isn't clear what is being modeled in this system. • The effect of old and young sera could be a consequence rather than the cause of aging. Indeed, serum composition is likely changing with age and thus old serum is less competent to support cellular activity when compared to young serum. However, this is a cell culture issue and not really an aging process. • The data are interesting, but the overall focus/direction of the application does not support product development. The data provide a solid basis that the current prototype could be used to study the mechanisms by which serum from old and young patients can affect cellular function. However, none of the current data demonstrate that industrialization of this prototype could work. • Why does the proposal focus on the liver/adipose axis? The interaction between the liver and fat tissues is not the most obvious inter-organ interaction in aging. The liver is not an organ that ages very strongly compared to the brain or muscle. Metabolism is important, but so are many other mechanisms (DNA repairs, environmental factors, etc.). • The chip will contain cells derived from hiPSCs. The effect of young vs old serum on these cells might be difficult to interpret in the context of aging. • Because cells are usually exposed to interstitial fluid (ISF) and not serum in vivo, a panelist suggests replacing serum with ISF, such as hepatic lymph, in the system. While serum and ISF share many components, concentrations vary by large amounts that are relevant to cell signaling. • The organ-on-chip works well but checking the quality of the cells grown in this system is essential. Unfortunately, this piece is missing from the proposal.
GWG Votes	**Is the project well planned and designed?**
Yes: 6 **No:** 7	• The experimental designs are rigorous, with both gain- and loss-of-function experiments. The applicant not only induced aging but also showed that their aging read-outs can be reversed. • The two-year timeline is appropriate. A shorter time frame would be impossible. Each differentiation takes between 10-25 days. • The project plan is a weakness of this application. The progression to large scale production seems poorly planned. There is no plan to produce the cells, which are the most essential part of this system. This application is mainly an academic exercise that is exciting in its own way. But, it's not really adapted for product development leading to a device used for broad end use. • The effort to make the prototype into an all-user system should occur prior to, rather than after, confirming the impact of donor age in the system. Otherwise, there is a major risk that data generated in Aim 1 will not be reproducible. This part needs to be reinforced. Asking future users to simply use a commercial kit to produce the cells is unlikely to be successful. The phenotypic assay look incredibly complicated and not compatible with high throughput applications. • It is not clear how the tool would be ready for commercialization at the end of the project. • The articulation between the two aims is not adequate. The academic importance cannot be questioned, but the industrial/application aspect is definitely neglected.
GWG Votes	**Is the project feasible?**

Yes: 9 **No:** 4	• The project is feasible. • The team has impressive experience and successdsad. They have all the expertise on aging necessary to develop an exciting research program. Additional experience in cell differentiation could be useful. • The environment seems very strong, and all the resources necessary to develop this program are already available. • The timeline seems reasonable for Aim 1 as all the reagents are already available. The use of commercially available sera is helpful. Nonetheless, the use of different hiPSC lines could take more time than initially planned as variability could be a key issue. • The application lacks a lot of timeline detail. • The team does not appear experienced in product development. • The three identified risks in the proposal are vague, e.g., "troubleshooting will be needed." • There is a very limited contingency plan. What happens if the new chip does not work, if the new protocol for liver differentiation fails, if new hiPSC lines give opposite results, etc.?
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12 **No:** 1	• Ethnicity and sex diversity are a key focus of the proposal. The applicant will address these key factors in aging by using sera from a diverse population of donors and hiPSCs with different genetic backgrounds. The number provided, while limited, seems enough to interpret data. • The project is designed to include all the diversity of California population. • Yes, it upholds DEI principles. • Outreach/education efforts are not addressed in the application.

Application #	TRAN1-17005
Title (as written by the applicant)	A humanized monoclonal antibody for the therapy of acute kidney injury and chronic kidney disease
Translational Candidate (as written by the applicant)	Humanized monoclonal antibody targeting human ENPP1 (ectonucleotide phosphatase/phosphodiesterase-1)
Area of Impact (as written by the applicant)	Kidney disease
Mechanism of Action (as written by the applicant)	The therapeutic candidate mediates a metabolic rescue of human renal progenitors after acute or chronic kidney injury. This results in decreased cell death of renal progenitors and increased proliferation. Overall this results in enhanced renal regeneration and repair with better preservation of kidney architecture and significant preservation of post injury kidney function.
Unmet Medical Need (as written by the applicant)	The human kidney is a terminally differentiated organ and incapable of robust regeneration. Chronic kidney disease (CKD) is an enormous public health problem that affects 15% of the population in the United States and globally affects more than 800 million people. The product targets a key protein that plays a pivotal role in contributing to metabolic aberrations after kidney injury, and will be a novel drug for acute kidney injury and chronic kidney disease.
Project Objective (as written by the applicant)	Pre IND meeting
Major Proposed Activities (as written by the applicant)	• CMC: Upstream and downstream development • CMC: Research cell bank construction • CMC: Master Cell bank Construction • Pharmacology: Pk and dose finding studies • Safety: Pilot Safety Studies • Regulatory: Pre IND dossier prep and DEI training for Increasing diversity in clinical trial recruitment
Statement of Benefit to California (as written by the applicant)	Chronic kidney disease (CKD) is one of the fastest growing non-communicable disease in the US and the 9th leading cause of death in California. The number of people living with kidney failure in California has increased by 45.7% since 2009 and more than 80,000 people in California undergo dialysis. There are no pharmacological agents for CKD and the proposed therapeutic product would be the first in kind for the treatment of kidney injury and CKD and would thus have enormous impact in the state.
Funds Requested	$4,893,012
GWG Recommendation	***(1-84): Not recommended for funding***
Process Vote	*All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG."* *Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."*

Scoring Data

Final Score: 60

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

Mean	64
Median	60
Standard Deviation	6
Highest	80
Lowest	60
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

Key Questions and Comments

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

GWG Votes	Does the project have the necessary significance and potential for impact?
Yes: 7 **No:** 6	• The applicant has applied for a TRAN1 grant to further develop proof-of-concept for a humanized monoclonal antibody (anti-ENPP1) to inhibit the effects of ENPP-1, a protein that is upregulated during acute and chronic kidney disease. The applicant presents a compelling argument as to why a treatment for acute and chronic renal disease is necessary and has the potential to be highly impactful for public health. Chronic kidney disease (CKD) is thought to be prevalent in 15% of the US population with more than 800 million people estimated to have CKD worldwide. Approximately a million people in the Unites States alone have kidney failure, and more than half a million people in the United States are on dialysis. The disease is also associated with high racial and ethnic disparities. Black Americans comprise only 13% of the US population but account for more than 35% of Americans with kidney failure and are 4 times more likely than Whites to develop kidney failure. • Kidney transplantation is not an option for many candidates, and out of the nearly 100,000 individuals awaiting kidney transplant, only 0.5% obtain a kidney from a living donor, representing a large unmet clinical need. • Approximately a million people in the Unites States alone have kidney failure, and more than half a million people in the United States are on dialysis. The potential for a novel treatment has the possibility for immense impact. • If successful, the product could reduce the demand for kidney transplants. These are a major medical burden. • The value proposition is impactful. Reducing kidney cell damage in acute injury and chronic disease via a biologic would represent a practical and cost-effective way to improve patient outcomes. • There are few effective therapies for acute kidney injury and chronic kidney disease. A biologic to reduce damage associate with kidney disease would have a significant impact on kidney disease. • The promise of an agent to augment renal progenitor cell survival and proliferation to improve renal outcomes in acute kidney injury (AKI) and CKD is not novel, though the selective targeting of ENPP1 to effect this change is. • The proposal claims that the candidate acts on renal progenitor cells, but these claims are not convincingly supported. The target cell type is unclear. • The limitations of the animal models weaken the arguments for further development using these models alone (particularly the nephrotoxic diet model). • Given the multitude of redundant and complementary pathways for damage and repair in the kidney, it is unlikely that targeting a single gene will have meaningful clinical outcomes.

	• Given the limitations in the rationale, it is unclear whether the proposal is actually a stem cell application. All of the therapeutic effects could be unrelated to renal progenitor cells. • The investigators cite a correlative analysis of ENPP1 expression and CKD that does not appropriately represent the most common causes of CKD (Diabetes Mellitus and hypertension).
GWG Votes	**Is the rationale sound?**
Yes: 3 **No:** 10	• Preliminary data provided by the applicant show a reduction of kidney cell death in a human iPSC kidney organoid model of kidney injury. • Preliminary data also show a slight decline of renal damage in a mouse kidney injury model. • At a micro view, the data are supportive. • The rationale is not completely robust. The most compelling data is loss-of-function data that show elimination of ENPP1 resulted in renal function improvements following toxin-induced injury. The effects on purinergic danger associated molecular pattern (DAMP) signaling/metabolism are less convincing. The ENPP1 targeting data in ENPP1 humanized models are also less convincing because the anti-ENPP1 monoclonal antibody used is target specific, and the models are not physiologically relevant. However, the rationale is sound with respect to the several small human data sets demonstrating increased ENPP1 expression in patents with CKD compared to healthy controls. Moreover, the correlation between the degree of ENPP1 expression in the kidneys and their glomerular filtration rate (GFR), with higher ENPP1 expression associated with lower GFR, suggests therapeutic potential of an anti-ENPP-1 to improve renal function. • The data providing the underpinning for the translation plan are concerning. Specifically, the dietary renal injury model for a therapeutic that targets the ENPP-1 pathway are not convincing. The other unilateral ureteral obstruction model is interesting, but uncommon clinically. Further, the data aren't very compelling, showing a small reduction in fibrosis. In this panel, there was no mention of efforts to reduce false discovery such as unbiased stereology. The latter should be standard. The lack of rigor in this area is a moderate concern. • The Target Product Profile (TPP) states the initial base case will be patients with AKI. They describe a global non-profit that creates/implements clinical practice guidelines for kidney disease [redacted] Stage 1 patients. The issue with this target patient population is that the overwhelming majority of patients with stage 1 AKI resolve spontaneously, and within 48 hours. The best example of this is in trauma/hemorrhagic shock induced AKI, and along with sepsis these form the two leading causes of clinically relevant AKI. It is incumbent upon the applicant to have a model that demonstrates how this may be generalizable to the larger populations of clinically relevant AKI. • The statements leading off the proposal are difficult to reconcile with the planned mechanism of action (MOA) being the site of benefit. The applicant states that the adult mammalian kidney has limited regenerative potential, presumably due to limited renal progenitor cells (RPCs) or the lack of induction of RPCs. However, it is unclear how the plan to use the proposed metabolic strategy that limits purinergic DAMP induced signaling would induce RPCs. Figure 1 from Reference 1 in the proposal states: "At present, however, it remains an unsettled controversy as to whether the adult mammalian kidney contains self-renewing renal progenitors or can be induced to form cells that exhibit stem cell-like behaviors in the context of renal injuries and other disease conditions". Fundamentally, the proposal relies on the congruence of the rodent data and potential translation to humans based upon *in vitro* work. It is likely that the data showing cellular toxicity induced by ENPP would reproduce with most cell types (as the authors note), since this is a conserved damage response. • Somewhat, but not to the degree one would expect. There are concerns about the range of other proinflammatory pathways in the DAMP signaling that function in parallel to the purine signaling pathways that this won't impact. This includes reactive oxygen species (ROS), peroxisome proliferator-activated receptor gamma (PPAR-γ), among others.

	• Single DAMP interruption using monoclonal antibodies (MoAbs) was a very popular approach in critical care since the late 1980s. Much of the discussion around the failures of these strategies surrounds the multi-faceted inflammatory cascades that surround ischemia-reperfusion and sepsis driven DAMPs such that a single pathway strategy rarely translates into a success. • The model system might not be relevant to the target disease. • The data presented to support this science may be scientifically flawed and reflect other pathways in the body. • The premise that ENPP1 inhibition can influence metabolic damage in kidney disease is supported by known toxicity of AMP that is converted to adenine which disrupts pyridine biosynthesis. The proposed molecular mechanism of action is sound, but it is noted that redundancy might complicate targeting this pathway as a therapeutic strategy. • Available data suggest an increase in expression of ENPP1 in renal progenitors but do not establish that the mechanism of action is on renal progenitors. A progenitor-specific knockout/knockdown or other targeted approach is necessary to establish the target cell type; ENPP1 is expressed in many tissues and multiple cell types of the kidney. • Animals treated with their therapeutic mAb following renal injury from the adenine-rich diet had improved fibrosis scores and renal function. The effect in the [redacted] model was less convincing. In addition, the knockout (KO) ENPP1 mouse exhibited a modest improvement in renal histology and function compared to controls. • Using [redacted] as a marker of RPC is flawed; this same protein gets upregulated in sublethally injured proximal tubules.
GWG Votes	**Is the project well planned and designed?**
Yes: 6 **No:** 7	• Activities in goals 1 and 2 are well-aligned with the pre-IND objective of the project. Similarly, the monoclonal antibody (MoAb) upstream and downstream manufacturing processes and biophysical characterization assays are standard in the field. • Yes, most of the work is in scale up of the MoAb production with appropriate pharmacokinetic-pharmacodynamic (PK/PD) testing etc. • PK, dosing, mechanism of action, and safety studies are also appropriate. • Sufficient details are provided for PK, dose-response, mechanism of action, and safety studies. • Most of the work is in scale up of the MoAb production with appropriate PK/PD testing, and a pre-IND meeting with the FDA to discuss IND enabling studies is appropriate. These objectives appear to fall in line with next early-stage development. • The planning and testing of the MoAb for commercialization is well-organized from a characterization, toxicity, and regulatory perspective. The capacity to enroll diverse patients using existing institutional resources and cohorts is a strength. • Consideration of complementary humanized mouse models is a strength. • Off-target toxicity is well considered including use of humanized mice and a relevant preclinical model. • There is little consideration of quality by design (QbD) principles. Critical process parameter effects on critical quality attributes are not clearly defined or related. Design of experiments approaches are not employed. • General approaches described in the plan lack key specifics, especially in the manufacturing aspects. For example, it isn't clear what will be varied to optimize upstream and downstream processes, or what formulations and stability assays will be used. • It is unclear why the planned use for this isn't around areas like renal transplantation, cardiac surgery with known incidence of AKI, thoraco-abdominal aneurysm repair with known renal ischemia due to cross clamp, with the ability to pre-treat and prevent AKI rather then going after CKD with established fibrosis. It is also unclear how activating tubular RPCs will alter interstitial fibrosis. • The team would benefit from including a kidney expert.

	• The adenine diet animal model is not considered among the most widely used and accepted models of AKI or CKD. There is no accepted model for AKI used.
GWG Votes	**Is the project feasible?**
Yes: 10 **No:** 3	• The proposed MoAb and the methods for cell and animal model testing are in hand. The investigators, who bring substantial prior experience from a previous CIRM award, are well-qualified for this work. Additionally, the contract research organizations (CROs), contract development and manufacturing organization (CDMO), resources, and facilities involved in the project are exceptionally strong, providing a robust foundation for successful research and development. • Their development plan seems robust, and they have aligned with the relevant CROs to take the project to the next level of translation. • The applicants carefully account for time delays in nonclinical testing if toxicology batch lots are not ready on time. They factor in a cost of the potential delay. • The milestones appear achievable. • Some milestones need quantification. For example, it is unclear what the critical quality attributes (CQAs) and the associated release criteria are. • Additional nephrology expertise may strengthen the team's ability to choose the appropriate models for pre-clinical validation. • Failure to have an expert on basic and translational AKI and CKD on the project raises questions about its feasibility.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12 **No:** 1	• Yes, renal disease disproportionately impacts underserved communities. • DEI is the most developed part of the application, presumably due to their prior experience with CIRM applications. • Kidney disease disproportionately affects underserved racial/ethnic communities, especially African-Americans. The product could address this disparity. • The team will engage advisory boards and devise strategies for recruitment from diverse communities for clinical studies in the later stages of this project. • The applicants plan on health equity community engagement. These activities primarily involve community engagement and outreach, establishment of a community advisory board (CAB) and clinical trial education planning for DEI. A separate budget focused on these activities has also been proposed. They also plan on a diversified targeted recruitment program for Phase 1. • The application includes impressive institutional resources, consultants, and community engagement to uphold DEI principles. • The project plan does not account for sex as a potential biological variable in the mouse study, and the number of male and female animals in the primate study is too small to identify potential differences.

Application #	TRAN1-17059
Title (as written by the applicant)	Engineering iPS Cell-based Therapy for Parkinson's Disease
Translational Candidate (as written by the applicant)	Dopaminergic (DA) neurons
Area of Impact (as written by the applicant)	Brain repair strategies in Parkinson's disease, image guided cell delivery into the brain, restoring brain function after neurodegenerative disease.
Mechanism of Action (as written by the applicant)	Since Parkinson's disease stems from the degeneration of one cell type, the dopaminergic (DA) neurons, in a defined brain location, the mechanism of action of the grafted DA neurons into the target brain location is DA cell replacement to reinnervate and provide regulated release of dopamine in the striatum, restore dopaminergic function.
Unmet Medical Need (as written by the applicant)	Approximately 94,000 people suffer from Parkinson's Disease in California, while in the USA, it is over 1 million and 90,000 new cases are diagnosed each year with an estimated cost of $27 billion per year. All available treatments are symptomatic and lose efficacy over time with unbearable side effects. No alternative disease modifying treatment exists.
Project Objective (as written by the applicant)	Perform IND-enabling studies for Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Generate cGMP-compliant cellular product (dopaminergic neurons). • Complete the FDA-requested biocompatibility and sterility testing on clinical delivery device. • Complete the FDA-requested safety and efficacy studies with the cellular product and delivery device. • Regulatory & Clinical Strategy, prepare and submit Pre-IND package, conduct Pre-IND meeting with the FDA.
Statement of Benefit to California (as written by the applicant)	In California, approximately 94,000 people suffer from Parkinson's disease with no curative treatment options. We are developing a disease modifying therapy for treating patients with PD. The CIRM award will accelerate our progress toward offering this therapeutic option to California patients and commercializing the novel cellular product and intervention. The award will also expand our intellectual property portfolio and significantly benefit Californians and the state's economy.
Funds Requested	$4,501,206
GWG Recommendation	***(1-84): Not recommended for funding***
Process Vote	*All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG."* *Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."*

Scoring Data

Final Score: 60

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

Mean	58
Median	60
Standard Deviation	9
Highest	75
Lowest	50
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

Key Questions and Comments

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/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:** 7	• There are currently more than 1 million people in the US suffering from Parkinson's disease (PD). While there are a number of pluripotent cell-derived dopaminergic neurons or their precursors currently in clinical trials, efficacy data are scant. Therefore, this product could impact this unmet medical need. • If successful, this product along with others being developed, could significantly impact patient care. The economics of producing a cell therapy for PD are unknown, but a cell replacement therapy would seem to be the only way to actually replace the dopaminergic neurons lost in PD. • This is a significant disease. • No meaningful changes were made to the application in response to review comments.
GWG Votes	**Is the rationale sound?**
Yes: 6 **No:** 7	• Whether the specific source of iPSC the applicant uses is important in the derivation of dopaminergic cell types is unknown. A seed bank of the cells has been made, and differentiation into neural stem cells (NSC) in suspension culture which is scalable has been achieved. These cells can be further differentiated into TH+ neuronal cells. • In vitro and in vivo histological data indicate the development of cells producing TH as well as other markers expected to be found in DA neurons. In addition, there are supportive data from a rat model of PD as well as two relevant preclinical models of PD showing some efficacy in the rat model and one of the other models while showing survival of TH+ neurons in the other model. The applicants have also developed a device for MRI-guided delivery of the cells without the use of a stereotactic frame. • The rationale for using intermediate NSCs remains unclear.
GWG Votes	**Is the project well planned and designed?**
Yes: 1 **No:** 12	• Currently there are significant hurdles to CMC goals. It is unclear that the issues identified by FDA feedback have been or can be addressed. • Responses from the applicant team seem to overreach (e.g., guaranteed purity for a cell therapy). • The bulk of the program involves making various GMP cell banks and testing the final product in pre-clinical animal models for safety, efficacy and tumorigenicity with the aim of submitting a pre-IND to FDA. • There appears to be quite a bit of redundancy in terms of the number of GMP banks that will be made. The plan is to make 3 GMP MCBs from the current seed bank. From the 3 MCBs they plan to make 3 WCBs. From the 3 WCBs they plan to make 3 NSC MCBs and from the 3 NSC MCBs they plan to make 3 NSC WCBs. From the NSC banks they

	plan to make 3 lots of 100 vials of product. That is a lot of work and quality testing and quite redundant. • FDA has stated they will require adventitious agent testing on any MCB as well as limited testing based on reagents used on any downstream banks. This testing is quite expensive for the MCB and can't be justified for 3 banks. • The main issue that might come up in making the various banks is abnormal karyotype. Given that, they could make one iPSC MCB from the seed bank, test karyotype, and, if it is normal, produce a WCB (perhaps more than 100 vials – more like 300). Again, I would test the karyotype and, if normal, proceed to making a NSC bank – I would not make a NSC MCB and WCB – just a NSC WCB. Again, test karyotype and if it is normal make the product cell bank. All the other testing call follow once the banks are made. • In addition, FDA have requested donor eligibility testing to be done at the time of cell collection or [redacted] days before or after; it is not clear that was done. The publication provided to FDA mentions the use of supra-paramagnetic beads as a contrast agent for MRI imaging. It is not clear if these beads will be used in the clinic, but, if they are, FDA has asked for more information (question 6). • While the project is well constructed, there is not enough detail to assess whether the applicant understands what FDA is requesting.
GWG Votes	**Is the project feasible?**
Yes: 2 **No:** 11	• The project is feasible, although the team's lack of experience with FDA development pathways is evident. • The regulatory package is poor, as indicated by the FDA referring the team to OTAT Learn for assistance with preparing appropriate submissions. • If the applicants pare down the cell banking and pay close attention to the FDA comments, the proposed milestones are achievable. • Currently there are significant hurdles to CMC goals. It is unclear that the issues identified by FDA feedback have been, or can be, addressed.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 11 **No:** 2	• Yes I believe the institution is well versed in this area and the applicants have taken account of race, ethnicity, sex and gender diversity. • The aim is to include diverse populations in the recruitment process when a clinical trial is approved.