APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Resubmission	Previous CIRM Funding	Disease Indication	Product Type	Approach
TRAN1-13342	Optogenetic therapy for treating retinitis pigmentosa and other inherited retinal diseases	**$3,999,553**	**Y**	**90**	90	1	85	90	14	0	Y	N	Retinitis pigmentosa	Gene therapy	Delivery of light sensing channelrhodopsin to retinal cells
TRAN3-13332	Living Synthetic Vascular Grafts with Renewable Endothelium	**$3,112,567**	**Y**	**87**	87	3	85	93	15	0	N	N	Kidney disease requirinf heodialysis	Medical device	Creation of a vascular graft that achieves rapid endothelialization for use in hemodialysis
TRAN1-13370	Next generation affinity-tuned CAR for prostate cancer	**$5,805,144**	**Y**	**85**	86	2	85	93	13	0	Y	N	Prostate Cancer	Cell and gene therapy	Development of a CAR Tcell therapy for prostate cancer
TRAN1-13345	Autologous MPO Knock-Out Hematopoietic Stem and Progenitor Cells for Pulmonary Arterial Hypertension	**$5,207,434**	**Y**	**85**	84	4	70	88	13	2	Y	N	Pulmonary Arterial Hypertension	Cell and gene therapy	Deletion of myeloperoxidase gene in autologous hematopoietic stem cells to reduce development of PAH
TRAN1-13296	Overcoming resistance to standard CD19-targeted CAR T using a novel triple antigen targeted vector	**$4,023,700**	**N**	**80**	79	6	60	85	1	13	N	N			
TRAN1-13313	Cone progenitor cells for prevention and treatment of retinal degeneration	**$800,000**	**N**	**65**	64	4	60	70	0	13	N	N			
TRAN1-13329	A gene therapy for producing COVID-19 prophylactic antibodies in immunocompromised individuals	**$5,282,750**	**N**	**63**	64	9	50	84	0	14	N	N			
TRAN1-13333	Neural Stem cell-mediated oncolytic immunotherapy for small cell lung cancer	**$5,088,499**	**N**	**60**	63	5	60	70	0	14	Y	Y			
TRAN4-13380	Vector Valley, CA: Establishing California as the World's Gene Therapy Foundry through the AAV Superproduction Process Node	**$1,067,050**	**N**	**60**	63	7	50	75	0	15	N	N			
TRAN1-13314	An Ocular Gene Therapy to Treat Dry Age-Related Macular Degeneration (AMD) - an Unmet Need	**$3,197,261**	**N**	**-**	-	-	-	-	0	14	N	N			

Application #	TRAN1-13342
Title (as written by the applicant)	Optogenetic therapy for treating retinitis pigmentosa and other inherited retinal diseases
Translational Candidate (as written by the applicant)	An AAV gene therapy delivering a light sensitive gene to treat patients with advanced RP.
Area of Impact (as written by the applicant)	RP is a genetic disease that causes retinal degeneration leading to near or complete blindness in most patients.
Mechanism of Action (as written by the applicant)	This therapy delivers a potent transgene with high sensitivity to light incoming to the eye, and high dynamic range. It has been shown to effectively treat the target retinal neurons. Light activation of the protein delivered by the product results in a signal being sent to the visual cortex of the brain.
Unmet Medical Need (as written by the applicant)	This product will treat patients with advanced RP and other IRD who currently have no other approved treatment.
Project Objective (as written by the applicant)	pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Preclinical animal studies to further evaluate safety and efficacy • Manufacturing process and analytical development • Preparation for a pre-IND meeting
Statement of Benefit to California (as written by the applicant)	RP is a progressively debilitating disease which leads to blindness. Of the approximately 10,000 patients living with RP in California, many have advanced disease, to the point of total loss of visual acuity. Most of these patients need to receive healthcare benefits, special living assistance, and suffer from loss of financial independence. This product represents a potential breakthrough treatment for a high unmet medical need for RP patients to improve their quality of life.
Funds Requested	$3,999,553
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	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 proposal have the necessary significance and potential for impact?
Yes: 13	• Retinitis Pigmentosa (RP) is a group of rare, genetic disorders that involve a breakdown and loss of cells in the retina — the light sensitive tissue that lines the back of the eye. There is a significant unmet medical need for new treatments for RP and related inherited retinal disorders (IRD). The applicant is working on a potentially curative gene therapy for RP and related IRD. • The proposal has high potential for significance and, if successful, will address an unmet clinical need. The proposed product does not aim to provide a restoration of vision, but instead to improve the ability of RP patients to navigate their environment. • The therapy being developed has the potential to be a one-time curative approach for treating RP and related IRD. If successful, this would lead to an impactful and practical value proposition for patients. • How does this technology and its approach differ from its competitor's? What are the advantages and differentiating factors for this product? This may be second to market. • It is not clear how this differs from a competitor study that is currently underway. • There is a large and diverse population that would benefit from an effective therapy. • Based on science, and clinical efficacy has already been demonstrated. • A one-time treatment would have significant impact for these patients. • This is a gene therapy that could make a significant difference in vision for RP patients. • Yes, there remains a large unmet need in RP.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• The proposed work is based on sound science. Developing an ophthalmic optogenetic therapy is both scientifically and clinically promising. In preliminary studies, over-expression of the improved channel opsin variant in the retina proved effective in ameliorating blindness in mouse models. • The applicants' discovery of a more light-sensitive channel opsin and their subsequent follow up studies strongly support the development of this product. • The applicants' prior gene therapy using an earlier version of this channel opsin was tested in the clinic. It was well-tolerated but had a minor safety signal. • Through mutagenesis of a recently discovered variant, the applicant has developed a 1000x more light-sensitive channel opsin to improve the utility of their approach. • The rationale of the proposal is sound. The applicant appropriately responded to critiques of the rationale from the previous round. • This application has sound rationale and strong preclinical data.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**

Yes: 13	• One of the major criticisms from the last submission was the perceived lack of adequate planning and the overly ambitious timelines. The applicants have taken note of this feedback and have re-written the section "Project Plan and Milestones." The newly written section is well-designed and well-planned, aiming for an FDA INTERACT meeting in Q3 2022.
	• The responses from the team have addressed our questions. More systemic and ocular immunogenicity assessments have been added. The team may want to also consider an electroretinography test for safety.
	• Yes. However, going forward the applicants still need to consider
	  ◦ whether the capsid is specific to retinal ganglion cells, or if other retinal cell types are infected
	  ◦ which subtypes of retinal ganglion cells are infected
	  ◦ if expression of vector in melanopsin containing retinal ganglion cells will affect diurnal/circadian rhythm in patients
	• The proposal is well-planned with the appropriate controls and mitigation strategies. I do notice, however, that a comparison between the new viral capsid developed in this project and its tropism for the eye with the previously developed capsids has not been carried out.
	• The resubmission demonstrates that the applicant has sought and incorporated expert advice on development of this product.

	• A more thorough consideration of timelines is included in this resubmission.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 13	• The proposal is feasible as it is based on strong preclinical data. • This is a highly qualified team, and the project appears to be well staffed with the appropriate resources. • The applicant has already initiated a collaboration with a contract development and manufacturing company, and several outside experts have advised on the plan. • Yes, the timelines seem reasonable, and the team has added a contract development and manufacturing company, although I can't find the name of the vendor.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	• This technology will serve the needs of underserved communities because RP has high prevalence in underserved, particularly Hispanic, ethnic populations. • This product would serve underserved and under-represented communities, but the applicant does not state this. Instead, the applicant provides a generic outreach plan without identifying underserved groups. I think the applicant understands the need to reach out to engage a diverse trial population, but I'd like to see an analysis of the trial's target populations so I can confirm that underserved, and under-represented, communities are included in the outreach plan. • The applicant intends to establish partnerships with organizations that can help with outreach. I would have liked to see names and descriptions of potential partners.
No: 0	*none*

Application #	TRAN3-13332
Title (as written by the applicant)	Living Synthetic Vascular Grafts with Renewable Endothelium
Translational Candidate (as written by the applicant)	LXW7 coated ePTFE vascular graft achieves rapid endothelization and improved graft patency by capturing endogenous endothelial progenitor cells
Area of Impact (as written by the applicant)	This technology will produce long-lasting vascular grafts with self-renewable "living" endothelium and improve dialysis patients' quality of life
Mechanism of Action (as written by the applicant)	The arteriovenous ePTFE dialysis graft approach is the most common form of vascular access for hemodialysis in the U.S., but has high failure rates. One of the major causes is the lack of a functional endothelium which is crucial to the prevention of thrombosis and stenosis. The LXW7 coated ePTFE graft will promote in situ endothelialization as the LXW7 works to increase the capture and binding of endogenous endothelial progenitor cells (EPCs) and endothelial cells (ECs)
Unmet Medical Need (as written by the applicant)	Globally, in 2018 it was estimated that there were over 2 million people who suffered from kidney failure. Patients undergoing hemodialysis often require multiple interventions due to graft failure. There is an unmet clinical need for long-term vascular access for hemodialysis patients.
Project Objective (as written by the applicant)	Pre-IDE meeting with the FDA
Major Proposed Activities (as written by the applicant)	• Manufacture, characterize, and optimize a viable prototype in making LXW7-ePTFE grafts and evaluate their properties in vitro • Evaluate the mechanism of action, function, and efficacy of LXW7-ePTFE grafts in small animal models • Investigate the short-term and long-term behavior and function of LXW7-ePTFE grafts in clinically relevant large animal models
Statement of Benefit to California (as written by the applicant)	Californians are at risk for kidney disease. 106,888 Californians are living with end-stage renal disease (ESRD, or kidney failure). Without treatment, dialysis or a transplant, ESRD is fatal. Only 1 in 7 California patients on the waiting list got a kidney transplant in 2020. Patients undergoing hemodialysis often require multiple interventions due to graft failure. Providing a durable vascular graft with long-term patency will allow reliable access to life-saving hemodialysis for patients.
Funds Requested	$3,112,567
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 87

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

Mean	87
Median	87
Standard Deviation	3
Highest	93
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 proposal have the necessary significance and potential for impact?
Yes: 13	• The project addressed an important clinical need, and the impact of the technology is likely to be high. • Fistula and other vascular access failures are a leading contributor to morbidity and mortality in patients facing end-stage renal disease (ESRD) and who remain on dialysis for longer times as kidney grafts are in tight supply, or the patients' other comorbidities rule them out as transplant candidates. • The proposed commercial development of a LXW7 coated ePTFE vascular catheter to be used in ESRD, will have a significant impact on an unmet need, that being delivery of a hemodialysis vascular access catheter free of thrombosis and infection. Thus, the proposal does have significant potential impact. • The proposed product is aimed to address an unmet medical need - the quality and durability of arteriovenous grafts in dialysis patients. • This is a great proposal. Reviewers were very encouraging of this project. • The authors briefly mentioned the human acellular vessel product by a company but did not discuss all the pros/cons and competitive advantage of their product-candidate over the other product.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• The proposed project is based on very sound scientific rationale. The preliminary data is very strong and the PI provides convincing data regarding the ability of LXW7 to attract endothelial cells and endothelial progenitor cells to a surface and promote endothelial proliferation. • The scientific rationale is sound. It is based on small molecule (ligand) LXW7, which is mobilized on biopolymer and selectively captures circulating endothelial cells. • The available data support that this technology could help immediately and also springboard the development of other biocompatible, endothelialized vascular contact devices for surgical use. • The rationale is sound and is based on a strong preliminary data. • The preliminary data support further development of the product.
No: 1	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 13	• The proposal is well-planned and well-written; the milestones are clearly outlined. • Further well considered experiments leading to an IDE are proposed in this grant and will help found the basis for regulatory approval. I doubt further studies will be needed to complete the application for human trials but a pre-IDE meeting will help assure this. • Small animal studies may not be necessary, a large animal model (pig) would address all necessary points for regulatory submission. • A concern is the utility of Milestone 4, investigating the effects of the LXW7-ePTFE grafts on capturing human EPCs/ECs in the immunodeficient NSG mouse inferior vena cava interposition model. It would seem that these experiments should be done in the setting of an immunosuppressed pig model. • I agree with the reviewer comments that they should consider whether the mouse studies are truly necessary to move forward to the next step in development. • Mouse model might not be necessary; it is recommended to employ a large animal model. • Potential sex-based differences were not addressed in the proposal. It is an important topic to address. Also, it is important to address how well this technology will work with endothelial cells from diseased patients. • Questions were raised around the consideration of sex representation in the rat animal models. • It is unclear whether the LXW7 coated ePTFE vascular catheter can maintain the endothelization of the catheter under high flows of hemodialysis. In other words, what is the long term durability of the device? This question is not addressed in this study.

	• More attention to future CMC issues is encouraged, including the reproducibility of current production methods.
	• A few things are missing in the CMC plan:
	  • the final form of the product is not described (terminally sterilized? If so, by what? suspended in solution?)
	  • the container for the final product (implantable device) is not described
	  • no plans for the stability of storage of the device in the container

No: 1	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 13	• Clear steps in device design optimization are outlined. The team is experienced with other recent related product under development by CBER and CDRH under IDE/PMA development routes. Core resources are available at their institution which is well known in the area of surgery and device development. • The proposed milestones appear feasible. The team is qualified to perform the proposed work. • The timeline is reasonable. • The project is utilizing a relatively simple technology based on the established clinical practice, which increases its feasibility. The final version of the device should be better defined.
No: 1	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 12	• The technology is highly relevant to the underserved community. • This will especially help in populations with high frequencies of ESRD (black, hispanic, and white populations in rural areas) and also in women, who have smaller vessels and are prone to more severe problems with vascular access.
No: 2	• More attention needs to be applied to sex differences in the animal experiments.

Application #	TRAN1-13370
Title (as written by the applicant)	Next generation affinity-tuned CAR for prostate cancer
Translational Candidate (as written by the applicant)	A next generation cell therapy product that targets prostate cancer cells
Area of Impact (as written by the applicant)	Prostate cancer
Mechanism of Action (as written by the applicant)	The therapeutic candidate when expressed on the surface of immune cells allow them to binds to a protein that is overexpressed on the prostate cancer cells and kills them.
Unmet Medical Need (as written by the applicant)	Prostate cancer is the fourth most common cancer globally and the second leading cause of cancer death among men in the United States, with a 60% occurrence rate in men over the age of 65. Approximately 61,860 patients are expected to die from prostate cancer in California in the year 2021.
Project Objective (as written by the applicant)	pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Generate GMP compatible lentiviral vector encoding the therapeutic candidate • Process development and scale up for cGMP manufacturing of the therapeutic candidate • Rodent studies to determine the efficacy and safety of cGMP manufactured therapeutic candidate
Statement of Benefit to California (as written by the applicant)	Californians will benefit in several significant ways. Approximately 61,860 patients die from prostate cancer in California every year. If the therapeutic is successful, it will extend the long-term survival rates for Californians with prostate cancer. The proposed studies will have an added economic benefit for California by creating skilled jobs and new companies. The current therapeutic would also reduce hospital cost through improved efficacy and safety.
Funds Requested	$5,805,144
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	2
Highest	93
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 proposal have the necessary significance and potential for impact?
Yes: 12	• The significance of developing CAR-T based therapy for prostate cancer is high, as there is a lack of CAR-T based therapies for solid tumors. • Prostate cancer is the fourth most common cancer globally and the second leading cause of cancer death among men in the United States. There is a need for new, and potentially curative approaches, for treating prostate cancer. • Many men still die of prostate cancer, both old and young. Young black men are disproportionately affected. • The product is for metastatic prostate cancer which is incurable. • There are currently no immunotherapies for this disease. • The applicant is working on a CAR-T based therapy. The team is developing a potentially "one and done" curative therapy. • This product could provide a lasting cure for patients that are out of treatment options. CAR-T like therapies for solid tumors have a past history of lethalities, and the novel approach to the construct and it's modified signaling cascade may open the door to safer treatments for other solid tumors. • Great proposal with promise and worth funding, even though it might not actually go through to market.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• The applicant's main hypothesis revolves around the design of novel T-cell therapy to overcome the limitations of current CAR-T based therapies, with respect to safety and efficacy, in the context of solid tumors. The overall scientific rationale is sound. • The proposal revision has overcome the past criticisms and addressed how its quality attributes have been modified to provide a better discrimination between antigen on prostate cancer vs. antigen on normal tissues. Data gathered to date support steps towards an IND. • The applicant has generated a robust body of in vitro and in vivo data showing that their T cell-therapy is as effective as current CAR construct designs with the same target. • The rationale for the target is reasonable. • The novel strategy may be sufficiently different from other approaches with the same target. • The preliminary in vivo data are confusing as the "standard" construct has no activity in these studies. It is not clear why this is the case. Scrutiny of the data that will be generated by the proposed studies will be needed.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 12	• During the course of the proposed project, two important meetings are planned with the FDA. The first planned meeting is an INTERACT meeting. During the grant period, the team will submit a pre-IND briefing document detailing the intended scaled production process for the product and pilot data supporting the efficacy and safety of the product in preclinical models. Overall, this is a well-constructed, quality program. • The proposed studies will be sufficient for a pre-IND. • The experimental plan is well-outlined, the response to the previous review critiques is appropriate, but there are certain inconsistencies in the presented data. The mechanism of action is not well-understood. • Please ensure there are studies to assess off tumor binding using both TCR and cell microarray technologies. This should support the lower affinity binding avoids normal tissues, a key safety premise. • The novel assays that have been developed are of questionable utility.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**

Yes: 12	• The proposal is built on a solid foundation and is feasible. • The timelines are reasonable and appropriate. The applicant has considered and articulated a reasonable contingency plan to manage potential risks and delays associated with this program. • Various in vitro and in vivo approaches are in play to assess activity and safety in animal models of disease, and these kinds of data, while non-GLP, can be performed in a manner to include safety endpoints. These are often the types of studies which are suitable as "toxicity data" for CBER IND packages. Pathology should be added to point to lack of harm in normal tissues. • Yes, based on the preliminary data presented.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 12	• Prostate cancer is very relevant for the underrepresented communities, as the prostate cancer is often detected late in the course of the disease. • Yes, because many men are afraid to go to see their physician - this potentially gives late stage people a chance.
No: 0	*none*

Application #	TRAN1-13345
Title (as written by the applicant)	Autologous MPO Knock-Out Hematopoietic Stem and Progenitor Cells for Pulmonary Arterial Hypertension
Translational Candidate (as written by the applicant)	Autologous MPO Knock-Out Hematopoietic Stem and Progenitor Cells
Area of Impact (as written by the applicant)	Pulmonary Arterial Hypertension (PAH), initially associated with Scleroderma (Systemic Sclerosis-SSc), and then applied to other causes of PAH
Mechanism of Action (as written by the applicant)	Myeloperoxidase (MPO) protein produced by neutrophils plays a critical role in the development of PAH. Disrupting the MPO gene in autologous hematopoietic stem and progenitor cells (HSPC) followed by transplantation of the edited HSPC eliminates the source of neutrophil MPO. This approach prevents development of PAH in murine models and, we propose, in patients with PAH with Scleroderma (Systemic Sclerosis-SSc) and other forms of PAH.
Unmet Medical Need (as written by the applicant)	Pulmonary Arterial Hypertension (PAH) is a progressive condition for which there is no cure; existing treatments provide only symptomatic relief and survival remains unacceptably poor. Transplantation of autologous hematopoietic stem cells with MPO gene knock-out may be a novel treatment for PAH
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Assess PAH disease-modifying activity and safety of transplanted myeloperoxidase (MPO) gene knock-out HSPC • Develop cGMP cell manufacturing methods and analytic assays for MPO gene knock-out HSPC • Complete draft of clinical protocol and conduct pre-IND meeting with FDA
Statement of Benefit to California (as written by the applicant)	Pulmonary Arterial Hypertension (PAH) is a progressive condition for which there is no cure. We are developing a treatment for PAH by transplanting autologous HSC with MPO gene knock-out. The goal is to advance this novel therapy to clinical trials for PAH associated with Scleroderma, an auto-immune disorder often complicated by PAH. Scientific findings and biomedical materials produced from the studies will be publicly available to non-profit and academic organizations in California.
Funds Requested	$5,207,434
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	4
Highest	88
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 proposal have the necessary significance and potential for impact?
Yes: 13	• The project has a major significance for treatment of Pulmonary Arterial Hypertension (PAH) as this disease is currently incurable. If successful, the impact of this work will be high. • This proposal is aimed at the treatment of patients with PAH in the setting of Scleroderma (SSc). Given the potential of this therapy to have a beneficial effect on patient outcomes, and the poor outcomes of patients with SSc-PAH, this therapy has the potential to positively impact a currently unmet medical need. • This application focuses on a subset of PAH patients who also have SSc. The outlook for these patients is bleak. Given the poor outcomes currently for PAH-SSc patients, if successful, this strategy will certainly impact an unmet medical need. • The authors have bolstered their rationale from the initial proposal surrounding the justification for stem cell transplant (HSCT) in these patients, as well as bolstered the preclinical justification that this therapy may have a beneficial effect even in patients with established disease. • This is a modified stem cell product. There is evidence that knockout of the MPO gene can impact PAH by decreasing inflammation and fibrosis. It is unclear whether this is a one and done therapy or if repeat therapy will be needed and if so how frequently. In patients that have been newly diagnosed and are still in reasonably good health, I think there is a good chance that the applicants can develop a product that improves patient care. • Given the limited choice of other treatment modalities I do think this product can be impactful. The value proposition will depend on how often the therapy needs to be applied and what the cost of the therapy is - autologous cell therapies are normally quite expensive. • It remains somewhat unclear on the frequency with which HSCT is performed in SSc-PAH patients, and whether HSCT is feasible in patients with severe disease who are being put on the waiting list for a heart-lung transplant. This reviewer is concerned with the practical feasibility of enrolling patients for this trial, and would encourage the authors to think critically about the clinical trial design to ensure patients can be identified. • This was one of the weaker aspects of the proposal, because the potential applicability is limited.
No: 1	• The prognosis for patients is bad, however, this product is for a subpopulation of scleroderma who has PAH. The author proposes a complex solution involving ex-vivo, edited HSCT - a complex manufacturing and delivery process that will only be suitable to a minority of cases in which HSCT is medically ethical/indicated.
GWG Votes	**Is the rationale sound?**
Yes: 12	• The rationale of the proposal is solid. The applicant improved the description of the rationale in response to the critique of the previous submission. • The authors have improved the application with additional justification regarding the scientific and clinical rationale. They have addressed comments relating to the clinical patient population, and have clarified the preclinical mechanistic data supporting the project. • The data would be strengthened with preclinical animal data demonstrating that this product can reverse established disease in a suitable animal model; current data show only that the product can prevent the onset of disease. • There is animal data in rodents that show the knockout of the MPO gene can impact the disease, but the animal model relies on infusion of the product before the onset of the disease. That does not represent the real world situation. The applicants recognize this deficiency and are developing a rat model to test out treatment with the product after disease onset. It will be important to investigate whether this knock out strategy can reverse established disease in addition to inhibiting further damage. Animals with the MPO gene knocked out entirely develop normally so it would seem that selective knock out in HSCTs is unlikely to have any deleterious effect.
No: 2	• The resubmission still does not contain convincing data to demonstrate a potential therapeutic effect for established disease.

	• Unfortunately, this is a complex human disorder, and the parity with animal models of disease is poor. The appropriate dose and durability of treatment is hard to extrapolate from rodent models, making this an uphill battle with regulatory authorities. The fundamental problem is that treatment models should have been prioritized from the beginning, instead of prophylaxis models. • In such a complex disease, it is also a tall order to convince all involved that removing only MPO will be entirely sufficient to repair tissue. On top of this, it's the HSCT cells implanted that carry the therapeutic benefit, and they would need to distribute to the site of the lung and heart endothelium to carry out the therapeutic effect - this section was not apparently covered.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 13	• The proposal is well designed. However, mouse hypoxia model has limitations in mimicking human PAH disease. Also, an open question is whether the proposed approach can reverse the existing disease, and what would be the extent of functional recovery as a result of this therapy. Mitigation of potential problems is not well addressed in the proposal. • The applicants are part of another project that is CIRM funded and is in the clinic. Given that the current project has many of the same elements as the CIRM funded project, I do think they will be able to piggy back on that project and will be successful in doing all the activities required. • In some areas, like CMC, there are sparse details but given their previous experience with the regulatory authorities and the experience of the institution with cell and gene therapy, I think they will achieve the goal of a successful pre-IND meeting by the end of the project. • Overall, the program is well planned and designed. Regarding quality metrics and a formal QA/QC program, there is not sufficient information provided to make that assessment, although the experience of the prior cleared IND and support from the institution's gene and cell therapy program are promising.
No: 1	• This program has many good aspects, and the disease needs basic research and better animal models. This could be suitable for an earlier CIRM grant to develop these. The current best model was not discussed thoroughly and involved rats who are first allowed to develop vascular remodeling and PAH, then later treated with rat edited cells to see if disease can be reversed at the vascular level, and whether PAH and heart remodeling were reversed.
GWG Votes	**Is the proposal feasible?**

Yes:
14
	• The team is excellent and I think will be able to successfully complete the program.
	• Yes, but the treatment is hard and expensive to execute. It is likely to take an extra year to optimize the treatment models mentioned above and de novo rat model optimization can take more time than anticipated.
	• The proposal is generally feasible. However, enrolling a sufficient number of patients for the clinical trial could be challenging, because of the severity of PAH disease and the toxicity associated with the treatment.
	• The authors are encouraged to carefully consider the target patient population, and the feasibility of enrolling patients in this trial. It may be challenging to identify patients with SSc-PAH, who have severe disease to justify this experimental therapy, who do not qualify for a lung transplant (or are not sick enough to require one), and who also are healthy enough to withstand the challenges of a HSCT.
	• It is unclear what will occur if a specific patient's CD34+ cells are unable to be isolated, unable to be transfected, or otherwise fail release testing. It is unclear how these collective risks would be mitigated. It is also suggested to consider the overall risks of these concerns, coupled with other inherent risks of HSCT.
	• The timelines generally seem aggressive yet reasonable. Since a good bit of the CMC work appears based on a cleared IND, this is reassuring.
	• The authors propose 2 quarters for development of analytical assays for drug product release – this seems like an overly aggressive time-frame. Additionally, they do not state what release assays they intend to utilize, for either the drug substance or drug product.
	• In some areas like assay development I think they may have underestimated the time it might take to develop and qualify assays.
	• The contingency plan seems adequate. I think the main risks are:
	  ◦ Regulatory - FDA requiring more data - that really just means a time and cost delay.
	  ◦ Technical - Hard to predict what that might be until they get into the project but again, probably no show stoppers.

	• In the clinic later in the project they may also run into patient recruitment issues which again is just a time delay.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	• If this therapy is successful, the standard of care for the underserved community will be improved. • It appears likely that this product would enable the subsequent development of similar therapies that can effectively target the unmet medical needs of underserved minority populations. • Yes, I do think they have thought about this aspect, and while underserved communities are not at higher risk of PAH-SSc they would be more impacted by it. • The applicants have generally considered the needs of underserved communities in their application. • Potentially, in the sense that this is a potential one time fix. However, the HSCT still requires patients having access to a tertiary medical center, and resources to stay there during cell editing GMP work done. This still relies on a perfectly functioning medical system, and patients with an airtight referral network.
No: 1	*none*

Application #	TRAN1-13296
Title (as written by the applicant)	Overcoming resistance to standard CD19-targeted CAR T cell therapy using a novel triple antigen targeted vector
Translational Candidate (as written by the applicant)	A tri-specific CAR T cell therapy that will prevent relapse by targeting three different tumor antigens
Area of Impact (as written by the applicant)	Relapse associated with single or double antigen-targeted CAR T therapies
Mechanism of Action (as written by the applicant)	A single CAR T therapy able to target three different tumor antigens simultaneously will reduce the risk of tumor evasion and relapse associated with loss of a single antigen.
Unmet Medical Need (as written by the applicant)	Relapse from cancer due to antigen loss is considered a major impediment for CAR T therapy. Further, by targeting all three major tumor antigens, the transduction vector could be more widely applicable for many B cell malignancies.
Project Objective (as written by the applicant)	Data needed for pre-IND filing
Major Proposed Activities (as written by the applicant)	• Determine the efficiency, stability, and reproducibility of the DuoCAR vector in T cell transduction • Determine the specificity and efficacy of the DuoCAR T therapy versus conventionally used CD19 CAR T therapies • Identify potential off-target effects or toxicities of the DuoCAR T therapy using a closed Good Manufacturing Processes (GMP) system
Statement of Benefit to California (as written by the applicant)	Experience with commercial CAR T products has shown that access to CAR T therapy is a key bottleneck to equitable use of this life-saving intervention. The other major issue is efficacy and cancer relapse. Our institution has the largest geographic catchment of its peer institutions in California, enabling it to play a crucial role in enhancing California patient participation in stem cell trials. Development of a tri-specific vector also increases patient use by targeting a broader array of B cell cancers.
Funds Requested	$4,023,700
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 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	6
Highest	85
Lowest	60
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	1
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 12	• The significance and potential impact of the proposal are considerable. However, because there are several therapeutic products already available in this space, it will be important to demonstrate a substantial advantage of the DuoCAR T cell therapy over the existing CD-19 targeted CAR T cell therapies. • If successful, yes. In time, both resistance and durability will need to be addressed, but this effort should advance understanding. • The CD19/20/22 DuoCAR T cell therapy developed in the project is intended for non-Hodgkin lymphoma (NHL) and acute lymphoblastic leukemia (ALL) patients who relapsed or are refractory to at least two lines of therapy, including autologous and allogeneic stem cell transplant as well as standard-of-care CAR T cell products. NHL and ALL remain the deadliest forms of cancer and they need effective therapies. • By targeting three markers of malignant cells, the CD19/20/22 DuoCAR T therapy has the potential to kill B cells with any combination of the B cell markers that increase the remission rate. The product is intended to prevent the development of CAR T therapy resistance due to escape mediated by target antigen loss. If validated in the clinic, this multi-specific targeting CAR T approach may be expanded to other markers and cancer types. • The CD19/20/22 DuoCAR T therapy has the potential to overcome antigen loss-mediated relapse or the downregulation of target antigen in patients with B cell malignancies, which is an unmet medical need. • The high relapse rate after treatment with currently approved and marketed CAR T therapies has created an unmet medical need. The proposal aims to address the lack of durability of complete response after treatment with approved CAR T therapies. • The impact of the proposed work and product candidate is hard to estimate for the following reasons: (i) market entry will be challenging, as there are three CAR T therapies available for the same indications, (ii) if the proposed CAR T candidate reduces only a fraction of relapses it may not attain authorization for marketing, and (iii) there are several 'improved' CAR T therapies currently in development to address the same unmet medical need. • The regulatory pathway in the United States and strategy for point-of-care manufacturing are not fully planned. • Even though the concept of point-of-care manufacturing is very attractive and might be implementable via CIRM Alpha Clinics in California, the current Translation program is dedicated to necessary pre-IND studies and manufacturing issues. • The tough competition should be acknowledged.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• The rationale for developing the DuoCAR T cell product is sound. • Translation of nonclinical work to the clinic is never guaranteed, but to the extent possible, the background data support further development. • Other groups have successfully targeted CD19, CD20, and CD22 in CAR T cell therapies for B cell malignancies. Therapies that use these individual CAR T products in combination have been proposed and are in clinical trials for B cell malignancy relapse. This team has demonstrated in animal models the feasibility of combining three specificities in one CAR T cell and its efficacy in eliminating antigen-heterogeneous B cell tumors. • The rationale is sound, but it is worth noting that the proposed therapy only addresses the fraction of relapse that is due to loss of targeted (surface) antigen. There are multiple mechanisms of relapse after CAR T, including CD19+ relapses (with no loss of antigen expression) and immunologic rejection of murine components of the CAR vector. • The Target Product Profile (TPP) does not clearly specify the acceptable and estimated relapse rate reductions conferred by the DuoCAR T therapy.
No: 1	*none*

GWG Votes	Is the proposal well planned and designed?
Yes: 6	• The experimental plan is strong and well-described. However, the timeline of the proposed studies is tight, and it might not be necessary to perform this many experiments for the pre-IND meeting. • Yes. The project has three aims: 1) construct and validate the DuoCAR expression vector; 2) assess the efficacy and specificity of the DuoCAR T therapy against leukemia and lymphoma in vitro and in preclinical in vivo models; and 3) assess the efficacy and specificity of DuoCAR T cell product produced in the applicant's manufacturing system. • The CD19/20/22 DuoCAR T therapy has the potential to overcome antigen loss-mediated relapse or the downregulation of target antigen in patients with B cell malignancies, which is an unmet medical need. • The place-of-care manufacturing process has the potential of reducing cost and expanding the access of the therapy. • One suggestion for the team is to include studies with a more clinically relevant CD19 CAR T relapse animal model.
No: 7	• The therapy is targeted at reducing the incidence of relapse, i.e., this is the proposed major advantage over current therapeutic options. The data would be strengthened by examining the efficacy in a model of relapse, thus justifying the advantage(s) of this therapy over currently approved therapeutic options. • The proposal is very thorough. It may be possible to proceed to a pre-IND meeting more quickly through a more focused set of studies. The application should lay out the critical path and requirements for a pre-IND meeting, with a goal of moving to the clinic as quickly and safely as possible. • The applicants need to devise and test hypotheses for how and why the DuoCAR T therapy will outperform other, similar efforts. This will require preclinical studies in more relevant models. • If the proposed product candidate is intended to treat relapses post-(approved)-CAR T therapy, an animal model of this type of relapse should be included in preclinical studies. In these studies, Duo CAR T versus anti-CD20 and anti-CD22 therapies could be studied in mice with relapse after a 'standard-of-care' treatment with an anti-CD19 CAR T identical to and manufactured in a similar process to an approved, best-in-class therapy. • I recommend revision and resubmission.
GWG Votes	**Is the proposal feasible?**
Yes: 12	• The timeline is packed. An experienced group can achieve this timeline. But what is the critical path to a pre-IND meeting? • The team proposes to complete the project within 18 months, which is an ambitious and aggressive timeline. The project involves multiple rounds of animal studies and GMP production of live cells. There is no margin for error in the timeline. • The project involves a preclinical team at one institution and a technology team at another institution. Both the scientific rationale and DuoCAR technology platforms are from the technology team. The preclinical team will carry out some the in vitro and in vivo efficacy studies. The teams are well qualified for the proposed studies. The Stem Cell Program, Principal Investigator's lab, and multiple core facilities at the preclinical team's institution provide all the required resources and expertise. The technology team has a track record of carrying out its proposed studies with both internal and external resources and expertise. • One suggestion for the applicants is that they streamline the project, retaining only those preclinical studies that are on the critical path for regulatory approval. • The proposal appears feasible. The teams are well-qualified to perform the work.
No: 1	• The timeline seems too ambitious.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 11	• The therapy, if successful, will diminish the relapse rates in B cell malignancies, and thus will benefit underserved communities. • The DuoCAR T therapy will be produced using a place-of-care (POC) cell manufacturing system, which will lead to broader availability, which will benefit underserved patient populations.
No: 2	• The application does not adequately describe how this project would account for and address the needs of underserved communities.

Application #	TRAN1-13313
Title (as written by the applicant)	Cone Progenitor Cells (CPC) for prevention and treatment of retinal degeneration
Translational Candidate (as written by the applicant)	Cone Progenitor Cells (CPC): Adult stem cell-derived cones, the specialized nerve cells in the eye that mediate central vision
Area of Impact (as written by the applicant)	Reliable and safe manufacture of CPC is a critical bottleneck in advancing the cells to the clinic.
Mechanism of Action (as written by the applicant)	At minimum, CPC will have a potent neurotrophic (neuron-protective) effect: CPC are intended to protect susceptible (diseased) cone photoreceptors (and rod photoreceptors) from degenerating, losing function, and dying. In addition CPC will mediate cell replacement of lost cones in the retinas of treated patients, by integrating into the host retinas. The two effects are anticipated to slow or potentially reverse vision loss in patients with inherited retinal disease primarily affecting cones.
Unmet Medical Need (as written by the applicant)	There are no approved therapies for cone or cone-rod dystrophies - these patients have no options for vision loss. CPC alone have potential to slow or reverse blindness from inherited retinal disease (IRD), and in future, can be combined with other cell, gene, and drug therapies to address a wider range of blinding diseases.
Project Objective (as written by the applicant)	Readiness for transfer to Good Manufacturing Processes (GMP) manufacturing.
Major Proposed Activities (as written by the applicant)	• Tech transfer of lab-based manufacturing protocols to a manufacturing contract research organization • Aseptic and engineering campaigns of CPC manufacture
Statement of Benefit to California (as written by the applicant)	Californians with rare inherited retinal disease (IRD) have no therapies for slowing the unpredictable path to blindness, often at a young age. ConeSight's cone progenitor cells have potential to change this sad scenario. Although rare cone dystrophies are the first indication to be studied in clinical trials, cone replacement therapy will also be critical for addressing central vision loss in AMD, and our company will be working with California partner companies long-term to address this very common problem.
Funds Requested	$800,000
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: 65

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

Mean	64
Median	65
Standard Deviation	4
Highest	70
Lowest	60
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 9	• This program aims to use Cone Progenitor Cells (CPC) to treat inherited retinal diseases (IRD). Their first target population will be patients with cone-rod dystrophy (CRD) excluding Stargardt's CRD. While the targeted patient population is quite small, the indication is an unmet medical need. • The human CPC developed by the applicants would address a major unmet need in the treatment of IRD and CRD specifically, for which there are currently no treatments. • CRD is an important unmet medical need. However, for clarity, the application should more clearly differentiate the unmet need associated with CRD from the unmet need associated with age-related macular degeneration (AMD), a future potential direction for the program. • The approach of using CPC to treat IRD is novel; previous therapeutics have used other cell types. • The project aims to establish GMP manufacturing of the CPC product, cryopreservation, storage, and transport to a clinical site. The establishment of GMP manufacturing for this project is essential for it to move into clinical trials. If the candidate CPC therapy is successful in the clinic, further development of a CPC therapy that impacts various inherited eye diseases may be feasible. • If successful, the product could offer tremendous value to patients with a subset of IRD. • The project has high clinical significance and potential for impact, but technical issues in the proposed studies are limiting.
No: 3	• The application's preliminary data demonstrating disease modifying activity in vivo are limited.
GWG Votes	**Is the rationale sound?**
Yes: 7	• In principle, the scientific rationale is sound. The highly proliferative and differentiation competent CPC may be a useful source for regeneration of cone photoreceptor cells. However, the preliminary studies do not adequately demonstrate the degree of functional improvement in vision that the therapy might confer. • I can see reasons to believe that a successful transplant of CPC could ameliorate IRD – (i) through functional integration of the CPC and (ii) through the production of supportive trophic factors for existing cone and rod cells. • The applicants present preliminary small animal model data demonstrating that CPC can impact eye disease. The limitations are that rodents' eyes are functionally distinct and much smaller than humans' eyes, making dosage calculations complex. In correspondence, the FDA strongly suggested that the applicant conduct pre-clinical studies in a large animal model. The applicants are now planning non-human primate studies in addition to the studies proposed in this application. • I think the current data do support the development of the product. It will be interesting to see how the non-human primate studies turn out.
No: 5	• I agree with the FDA that the preclinical development in this program is at an early stage. The observed effects in the small number of treated rats (< 20) appear to be modest. This proposal does not include sufficient completed or planned preclinical model studies demonstrating efficacy to justify funding preparation for GMP manufacturing. More preliminary work is needed. • The concept of replacing cones with CPC in CRD is based on sound scientific and clinical rationale. The applicants present extensive preliminary data showing that they can generate CPC from donor eyes and that these cells engraft efficiently into the model rat and confer some improvement in vision. However, the degree of visual improvement compared to non-dystrophic model controls is unclear as the control data are not provided. • The dependence on a tissue source for CPC means that this approach is not scalable for commercial application, thus limiting its potential impact. The applicants suggest that they may convert to an iPSC source for generation of CPC. If they do, many of the completed and proposed studies will need to be repeated with the iPSC-derived CPC.

	• The application states the CPC are not well characterized at the message level and states that "comparative RNA-seq analysis is incorporated into the CIRM program." I could not find this in the project plan.
GWG Votes	**Is the proposal well planned and designed?**

Yes:
1
	• The FDA provided extensive comments on the Chemistry, Manufacturing and Controls (CMC) section of the INTERACT submission. The applicants do address the source and quality of the mAbs they use for sorting, but other FDA concerns about CMC are not sufficiently addressed in the application. I would like to see responses to all the FDA's concerns as this application is for development of a CMC package suitable for initiating clinical trials. In addition to full responses, the application would benefit from a table listing the points raised by FDA and the applicants' outlined plans for addressing each.
	• I think the timeline is quite tight - it certainly demonstrates urgency, but it may be off by three to six months.
	• The CMC section is currently not written for external evaluation so I cannot adequately review it. As examples,
	  ◦ The application indicates that cells are isolated from source tissue, dissociated to single cells, and expanded for two weeks. How is that done? In adherent culture or suspension culture? Are cells passaged during this period? If so, how? Are any growth factors used? What media are used? There are other examples, but I hope these will suffice to illustrate my point.
	  ◦ What about genetic stability of the cells? The cells are maintained in culture for 7 - 9 weeks. How many population doublings does that represent? Do the applicants take karyotypes to show that the cells are karyotypically normal throughout the expansion? How far can the cell culture expand before the cells accumulate abnormalities?
	  ◦ Is expansion necessarily limited to 100 million cells, or could the applicants expand to one or ten billion cells? Given the inherent differences in isolates I think it would behoove the applicants to estimate the number of clinical doses that could be manufactured from one isolate.
	  ◦ To my knowledge there should be no Oct4 positive cells in the preparations, so what does the observed Oct4+ population of 3% +/- 2% represent? Is there another method like immunocytochemistry that the applicants could use to cross-check the frequency of Oct4+ cells? Oct4 is a marker of pluripotent cells; the applicants should comment on this aspect of their FACS analysis.

No: 11	• The experimental details and the expected outcomes are not well-described. The FDA has asked for a non-human primate study, but such a study is not included in the project plan for this application. The preliminary animal model data are limited, and management of potential pitfalls is not adequately addressed. • I feel the applicants should not invest in preparing for GMP manufacturing before they conduct and analyze the non-human primate study (or similar study) recommended by the FDA. GLP-manufactured product should be sufficient for the toxicology studies. • The applicant company had a detailed INTERACT meeting with the FDA in July 2021 to seek guidance on the proposed development plan for CPC. While supportive of the general approach the FDA provided considerable advice on how the applicant company should proceed and what additional information would be required to take this product forward. The applicant company is addressing the FDA's recommendations both within and outside this TRAN1 application. However, it is difficult to fully assess the quality of the program as experimental details and detailed outcome measures are not provided. This can be easily addressed in a revision as the application currently has two and a half pages to spare. Additionally, some aspects that appear to be key for the IND, such as the non-human primate studies, are not part of this proposal.
GWG Votes	**Is the proposal feasible?**
Yes: 4	• The proposal might be feasible. However, the availability of tissue for obtaining CPC is not assured. If iPSC are to be used instead the project will become an early-stage discovery project. • The timeline may be a bit tight, but it's hard to judge based on the limited description of the manufacturing process in this application. • The team seems qualified. The contract research organization (CRO) the applicants have partnered with is qualified to do the cell manufacturing. • Most of the project will be conducted at the CRO, which does have the resources to complete the cell manufacturing aspects of the project. • I think the contingency plans are well-developed. One plan they mention is that to achieve commercial scale they may have to move to iPSC as the starting material. It would be

	helpful to know if the applicants or other research groups have previously made CPC-like cells starting from iPSC.
No: 8	• The applicant team does not seem fully staffed for the project plan. From what I can see, the CMC expert is a consultant who will commit 10% effort to the project. I recommend more total % effort from a CMC expert(s) plus additional regulatory expertise on this team. • I am concerned as to whether the team has the full necessary expertise to complete this study. • There are two primary phases: (1) complete technology transfer and feasibility run; and (2) engineer and optimize CPC manufacturing to prepare for GMP production. The second phase is dependent on the success of the first phase, but it is not clear that the technology transfer can be completed within the timeline proposed. • Addition of a statistician would benefit the rigor of the plan; currently statistical significance and data analyses are not described. • Given the importance of technology transfer and financing, I'm surprised the company Chief Financial Officer, or the Business Manager are not included as Key Personnel (and biosketches provided). • I could not find contingency plans to manage risks or delays in either the technology transfer or the optimization of engineering runs.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 4	*none*
No: 8	• The applicant does not address the issue of underserved communities relevant to this project. • The diversity plan provided focuses on the applicant company and its employees rather than the patient population. I don't think the issue of overburdened or underserved patient populations for this indication has been adequately considered. • They do not have well developed plans in this area. • This is not addressed in the submission.

Application #	TRAN1-13329
Title (as written by the applicant)	A gene therapy for producing COVID-19 prophylactic antibodies in immunocompromised individuals
Translational Candidate (as written by the applicant)	[Company Name] mAB-001
Area of Impact (as written by the applicant)	Therapeutic
Mechanism of Action (as written by the applicant)	This TRAN1 award would enable the rapid adaptation of our existing scale-up, development, and manufacturing process to the [Company Name] mAB-001 therapeutic candidate, positioning this candidate for Pre-IND, IND-enabling studies, and an IND filing with the FDA.
Unmet Medical Need (as written by the applicant)	Immunocompromised individuals who cannot benefit from COVID-19 vaccination
Project Objective (as written by the applicant)	Well prepared pre-IND meeting with the FDA
Major Proposed Activities (as written by the applicant)	• Animal Studies • Stability Toxicology • Chemistry, Manufacturing, and Controls (CMC), regulatory, and Pre-IND preparation
Statement of Benefit to California (as written by the applicant)	Vaccines do not confer protection to the sub-population of Californians who may be immunocompromised due to their advanced age or having a defective immune system. An effective non-vaccine prophylactic for COVID-19 could be of significant clinical benefit to people with high risk of severe COVID-19 disease, including ethnic minorities such as Black, Hispanic, and Asian groups. To address this unmet need, we developed a COVID-19 prophylactic strategy exploiting a gene therapy against the SARS-CoV-2 Spike protein.
Funds Requested	$5,282,750
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 63

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	63
Standard Deviation	9
Highest	84
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 proposal have the necessary significance and potential for impact?
Yes: 6	• Yes. Approximately 2% of the world's population mounts an inadequate immune response to a vaccine, including the COVID-19 vaccine. In the United States, approximately 7 million people are immunocompromised, including cancer patients undergoing chemotherapy, organ transplant recipients on medications, or people taking immunosuppressive agents for chronic diseases such as rheumatoid arthritis, multiple sclerosis and other autoimmune or inflammatory diseases. • The project addresses a significant problem. However, there are two outstanding vaccines for the COVID virus, multiple oral anti-viral agents, multiple monoclonal Abs, and a preventive drug. With that stated, I recognize that the applicants have proposed this study for the benefit of immunocompromised (cancer and solid organ transplant patients) and elderly patients. • The applicants have developed a delivery system for DNA cassettes that circumvent the dose limiting toxicities of other DNA-based systems. They already have an open IND for another project wherein a DNA cassette produces segments of the SARS-CoV-2 spike protein to induce an immune response. This current project aims to produce mAb fragments against conserved areas of the spike protein that bind and help eliminate the virus. While there are already mAb products on the market to treat COVID-19, the applicants claim that the current therapies have a shorter half-life than their candidate potentially has. • Yes. Monoclonal therapeutic antibodies are very expensive and work very well. Being able to make them more cheaply would be a great advantage. • The applicants' delivery technology is a potential platform for future therapeutics. • Yes, because I think the delivery technology is very interesting and could be used to deliver protein drugs to patients. However, I do not believe this application will lead to a successful product.
No: 7	• It's not clear to me that this product, if efficacious, would be superior to current therapies, even for immunocompromised populations. • The application does not provide compelling evidence that this gene therapy will produce therapeutic mAb fragments at levels sufficient to impact the course of COVID-19 disease. • The candidate may not prove competitive with easier-to-use therapies on the market. Relatedly, the application does not include rationale or evidence that this therapy will reduce any costs. • There may be therapeutic indications (other than COVID-19) that would represent a higher impact unmet need for this candidate therapy.
GWG Votes	**Is the rationale sound?**
Yes: 6	• Yes. This is a well written proposal that makes scientific and clinical sense. • It should be noted that the in vivo Pilot Safety #3 study the circulating levels of alanine transaminase (ALT) and aspartate transaminase (AST) need further interpretation. These levels are not in the normal range and indicate significant increases in these two biomarkers. Although it could be interpreted that the test article is causing liver injury, the AST/ALT ratio indicates acute muscle injury. • The rationale is sound.
No: 7	• I do think that the idea of introducing genes that encode mAbs has merit but there is a major problem with this candidate - mAbs currently in use are administered in doses of hundreds of milligrams or even grams. I can see this delivery technology being valuable for proteins that are needed in small quantities like some hormones and perhaps fragments of the SARS-CoV-2 spike protein to elicit an immune response. I don't see this approach as amenable to producing mAbs in bulk, as would be necessary. • I have major concerns about the difference between the mAb protein fragment concentrations produced by the DNA cassette system versus target therapeutic levels. The target therapeutic levels for treatment of SARS-CoV-2 are several 1000 mg of mAb, whereas the published reference indicate the DNA cassette system produces around 10 to 30 ug/ml. • It is unclear if this approach can lead to sufficiently high levels of mAb to impact the probability of infection or outcome. • Nowhere in the application does the applicant address the issue of how much protein/mAb this system will produce. I suspect it is in the microgram to milligram range -

	several orders of magnitude lower than would be needed to effectively eliminate a SARS-CoV-2 infection. • I think a major problem is that there are already a wide range of therapeutics for COVID-19, and the vaccine is very effective at lowering the risk of serious disease. • The applicants suggest using this candidate as a preventive therapy. I could imagine that working; in some cases, the therapy might produce just enough mAb to "nip it in the bud." Even so I think this would require much more mAb than their system can produce. • The applicants claim that this system will give durable expression of their mAbs and use a fluorescent reporter gene to show long term expression. It is hard to tell from the figure, but it appears that the luminescence has dropped to about 15-20% of peak values after five days. While there is some signal for up to one year, after a week or so the signal is quite low. Note: I do not know if, or how well, one can translate reporter luminescence to protein expression levels. • The data suggest that this expression system is interesting and may be useful for some proteins or hormones, but the data do not support the development of a therapy for COVID-19. • I would have loved to recommend this proposal if it included preliminary data showing efficacy.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 8	• Generally, the proposal is well-designed and well-written. However, the proposed small animal model is likely not to be appropriate for the newer SARS-CoV-2 variants. • For patients with COVID-19 who receive neutralizing mAbs, there is potential for the emergence of drug-resistant variants, especially when selective pressure is applied in the setting of drug treatment. The proposal needs to consider this very real problem - particularly in the target group of patients. • The applicants should clarify whether the focus of the project is to prevent infection, or severe disease. • The project plan is well done. It appropriately outlines (i) assay development and qualification, (ii) identification of additional suitable biomarkers to assess in vivo efficacy and safety, (iii) conduct of live SARS-CoV-2 challenge studies, and (iv) conduct of nonclinical PK/PD, ADME, safety, and stability preclinical studies to prepare for the pre-IND. • This was a beautifully written proposal.
No: 5	• The proposal is very well written. The delivery technology is novel and innovative. The issue I see is the small animal model, wherein SARS-CoV-2 has a very short half-life and the animals show few symptoms, as compared to humans. • As I mentioned above, I think this could be a useful technology platform for delivery of protein drugs that are needed at lower levels. • I think the outline of the project is reasonable but as mentioned above I think there is a fatal flaw. In all applications I am aware of mAbs are used in quite large doses - exceptions being drugs like Lucentis which are used very locally to treat AMD.
GWG Votes	**Is the proposal feasible?**
Yes: 7	• Overall, yes. However, the applicants may not be sufficiently familiar with the SARS-CoV-2 variants and their disparate pathobiology in small animal models. In the hamster model, it can be difficult to recover live Delta virus beyond 6 days; there is hardly any recoverable live Omicron virus; and the animals get few, if any, symptoms with either variant. In contrast there is observable disease activity (weight loss) in ACE2-transgenic mice, and these mice can be exposed to immune suppressive agents prior to infection. • The plan is well prepared and efficient.
No: 6	• It is not clear if sufficient levels of the mAb protein fragments can be generated in vivo to generate a therapeutic effect using this plasmid-based technology. The proposed approach is interesting and might be feasible if applied to in vivo production of other types of protein (outside of monoclonal antibodies). • I do not think the study is feasible, as described in my comments above. The animal model is not ideal. • No, I don't believe so. The central question is how much mAb do you have to produce in a semi-steady state to neutralize the virus? I would be astonished if this system will produce enough to have an impact given the very large amounts of mAb that are currently used in the clinic (they of course are bolus infusions).
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 9	• This is discussed in the proposal - COVID-19 burden is associated with poverty and social inequality rather than genetics. • The project is designed to address the needs of underserved communities.

	• I think they have done a reasonable job addressing the needs of underserved communities.
No: 4	• The underserved communities might be better served by the available COVID-19 vaccines. • it's not clear that people from underserved communities would choose this therapy over existing vaccines that are known to be safe and effective. • It is unclear if this therapy would truly have advantages over vaccination, aside from the theoretical justification that is provided. • I don't think that there is demand for COVID-19 treatments that are more complex.

Application #	TRAN1-13333
Title (as written by the applicant)	Neural Stem Cell mediated oncolytic immunotherapy for small cell lung cancer
Translational Candidate (as written by the applicant)	A clinically tested tumor tropic Neural Stem Cell (NSC) platform for effective distribution of oncolytic virotherapy to small cell lung cancer.
Area of Impact (as written by the applicant)	This NSC-delivered virotherapy approach will enable a more efficient, less toxic treatment for small cell lung cancer (SCLC) and chemo-resistant cells
Mechanism of Action (as written by the applicant)	LOAd703 is a replication-competent adenovirus with restricted replication and oncolysis to the dysfunctional retinoblastoma pathway, common in a wide spectrum of human tumors. We will use our tumor-tropic/penetrating NSC platform to produce the oncolytic virus within SCLC. Viral replication will lyse cancer cells and infect neighboring cancer cells, thus amplifying its effect until reaching normal tissue. We will also stimulate immune response to newly exposed tumor antigens.
Unmet Medical Need (as written by the applicant)	Most SCLC patients present late stage with extrathoracic metastases and can't complete chemotherapy due to severe toxicity and chemoresistence. NSC will more effectively target and distribute an oncolytic virus, electively lysing cancer cells and stimulating an anti-tumor immune response.
Project Objective (as written by the applicant)	Pre-IND meeting ready for Good Manufacturing Processes (GMP) clinical lot
Major Proposed Activities (as written by the applicant)	• In vivo determination of dosing regimen (multiple rounds) for maximal therapeutic efficacy • In vivo determination of secondary immune response following oncolysis of tumor cells • In vivo determination of preliminary safety / toxicity profile
Statement of Benefit to California (as written by the applicant)	Around 9,900 lung cancer patients are expected to die from lung cancer in California this year making it the deadliest cancer in California. SCLC is the most aggressive lung cancer with a dismal 6% 5 year survival rate. We anticipate that our stem cell-derived oncolytic virotherapy will lead to a more effective, less toxic treatment that will kill even metastatic foci and chemoresistent cells and improve the survival of SCLC patients in California.
Funds Requested	$5,088,499
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	63
Median	60
Standard Deviation	5
Highest	70
Lowest	60
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 8	• This project aims to target small cell lung cancer (SCLC) refractory to other treatment modalities with oncolytic viruses (OV) using a novel delivery mechanism – a Neural Stem Cell (NSC) line carrying the OV. The OV has been shown to lyse cell lines derived from different types of SCLC. If successful, this approach could have a huge impact on SCLC, which is very hard to treat. • This approach uses a banked NSC line to deliver a payload (an OV) to SCLC tumors in situ. If this project is successful, I do think it would improve patient care and give oncologists another tool in the fight against malignancies. • The manufacturing process is reasonably well defined but at this stage it is hard to judge what the cost of goods sold (COGS) might be for such a treatment. Thus, the value proposition remains unclear. Factors such as dose, number of treatments, and magnitude of response will all figure into the value proposition. • The potential clinical impact is high, but likely limited by multiple technical issues in the experimental strategy. • SCLC is one of the deadliest cancers with only 10–20% two-year survival. • The product may make systemic OV therapy feasible.
No: 5	• The data for an in vivo effect of this candidate are currently too limited for TRAN funding. • The target indication (SCLC) reflects an unmet medical need, but I have doubts about the success of the project. • The strength of this application lies in its attention to underserved communities. The institution's patient community well represents African Americans, Hispanics, and Pacific Islanders.
GWG Votes	**Is the rationale sound?**
Yes: 5	• OV have been around for quite some time and success in the clinic has been limited. Many patients have pre-formed antibodies to OV so the OV on its own can be rapidly eliminated. The thesis behind this project is twofold. First, loading the OV into a cell will protect it from pre-formed antibodies and therefore allow the virus to persist longer in the patient. Second, the NSC line is expected to home to tumor tissue and deliver the OV to the target site. The NSC are allogenic and may also be targeted by the immune system, but not before repeat dosing of the product. • Given the lack of animal models I think the limited data available do support development of the product. A similar product is already in clinical trials for glioblastoma. A recent report shows no real safety issues in that trial and while the numbers are small and there is no statistically significant effect, the data may eventually show a modest increase in survival times associated with the treatment. • In general, the rationale for the approach is sound. However, Milestone 4 ("determine the preliminary safety of IV-delivered LOAd703-NSCs using the optimal regimen") is not clearly laid out. A common approach to defining the safety of this type of therapy is as follows: (i) An acute toxicology study is conducted in wild-type mice, followed by repeat dose toxicology in wild-type mice and non-human primates. (ii) Biodistribution studies are conducted in tumor bearing mice, wild-type mice, and non-human primates. • There are data, albeit limited, that suggest this approach is promising. Unfortunately, given the mode of action it is hard to estimate how effective the product may be. For example, Figure 5 shows increased survival duration and decreased tumor growth in an NSG model treated with NSC loaded with the OV, but it is hard to interpret due to limitations of the mouse model. • It was curious to me that virus alone (in a dose 100-fold higher than in the NSC) had no impact on either survival or tumor growth. I guess it might be the targeting, but I would have thought the 100x higher dose would compensate?
No: 8	• In principle, the rationale is sound. However, oncolytic virus-based technologies have had limited success in the clinic so far. Addition of the NSC for targeting the virus to the SCLC might be a reasonable strategy, but preliminary data to support potential efficacy are limited. • I'd like to see some of the results from related studies before committing to this effort. It will mitigate risk and inform the design of necessary studies going forward.

	• The preliminary data have been further refined, but overall, the case for potential efficacy of the proposed product is not sufficiently convincing.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 3	• I think the project is well planned. All Chemistry, Manufacturing and Controls (CMC)-related activities will be handled by the Principal Investigator's institution, where there is a first-rate cell manufacturing facility. • I don't think they will face any unexpected news from the Food and Drug Administration (FDA) given that a similar product is already in the clinic for glioblastoma. Of course, nonetheless, we could better gauge the expected response from the FDA if the applicants conduct an INTERACT meeting. • While additional animal experiments could be done (e.g. using humanized NSG mice), these models are highly contrived and the window for experimentation is short-lived so I don't think these will add value. • I do think, however, that it is worth collecting more data from the ongoing trial in glioblastoma to detect any meaningful improvement in survival times. Otherwise, committing to this parallel path may waste resources.
No: 10	• My concerns relate to (i) insufficient consideration of biodistribution, (ii) insufficient data suggesting that the humanized mouse model will be useful in evaluating immune responses, (iii) the subtype of lung cancer in the immunocompetent mouse model, and (iv) unclear benefits of conducting the proposed RNA-seq studies. • The experimental strategy is appropriate, but there are few specifics provided. Limited efficacy data is presented. The applicant did not use all the provided space in the application to supply details of the approach. Description of the properties and safety profile of the NSC is also limited. • This application needs a reworked nonclinical plan to address interpretation of planned in vivo efficacy studies (i.e., how will these studies demonstrate the likelihood of clinical efficacy?), the potential immune response to this viral construct, and product biodistribution and safety in mice. • There is a lack of significant attention to safety issues. The applicant was not sufficiently responsive to the prior review. • The concerns raised by the previous critiques are not sufficiently addressed.
GWG Votes	**Is the proposal feasible?**
Yes: 10	• In principle, yes, but to recommend funding for this proposal I would need to see more data supporting practical feasibility. In my opinion, the current clinical trial of localized NSC OV delivery in glioblastoma should be completed before we fund this project. • Yes, based on the expertise of the investigators and the previous trials that have been carried out by the group. • Yes, but I recommend that the investigators consult with a toxicologist and nonclinical scientist. • Yes, I think this team is certainly capable of completing the milestones in a timely manner. • This team is well-qualified. The manufacturing group will certainly be able to produce material suitable for a first-in-human (FIH) clinical trial.
No: 3	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 10	• SCLC affects underserved communities at a high rate. Therefore, if successful, this therapy will address an unmet need within underserved communities. • Yes, this is addressed in the proposal. • Yes. This therapeutic approach would be much less expensive than current therapies and therefore more accessible to underserved communities. • Yes. I do think that since the last review the applicant has given more thought to underserved communities.
No: 3	*none*

Application #	TRAN4-13380
Title (as written by the applicant)	Vector Valley, CA: Establishing California as the World's Gene Therapy Foundry through the AAV Superproduction Process Node
Translational Candidate (as written by the applicant)	The AAV superproduction process is a tool for the generation of large quantities of high quality, potent AAV vector for stem cell and gene therapy
Area of Impact (as written by the applicant)	Supply bottlenecks for AAV are throttling clinical translation with wait times of 2-3 years and costs of $3-5M to produce vector for Phase I trials
Mechanism of Action (as written by the applicant)	The AAV "superproduction" process achieves 10-100x intensification of upstream production by expanding bespoke AAV producer cells to exceptionally high densities within our proprietary High Density Cell Respirator (HDCR) bioreactor and inducing packaging. The high titer AAV crude is then purified using established chromatographic approaches. This democratizes pharma-scale production capacity to academic researchers, patient advocacy groups, biotech startups, and other cell and gene therapy innovators.
Unmet Medical Need (as written by the applicant)	AAV-based gene therapies are routinely priced >$1M/patient due to inefficient and insufficient production. Radically improving the economics and logistics of AAV vector production is necessary for these breakthrough medicines to become nationally available and feasible.
Project Objective (as written by the applicant)	Design history file, tool ready for commercial use
Major Proposed Activities (as written by the applicant)	• Generate library of AAV producer cells spanning CIRM-relevant serotypes (e.g. AAV2, AAV9, AAVHSC) and beyond • Generate bespoke cell lines with genes-of-interest relevant to ongoing CIRM gene therapy initiatives • Superproduce AAV vectors using bespoke cell lines and supply to CIRM-funded initiatives for head-to-head comparison in stem cell models
Statement of Benefit to California (as written by the applicant)	Statewide access to the AAV superproduction process node will eliminate supply bottlenecks, enabling faster and broader pre-clinical and clinical testing of lead vectors, and accelerate the discovery of blockbuster medicines by encouraging risk taking and moonshots in academia and industry. The superior economics and logistics of the process will support more affordable and accessible medicines.
Funds Requested	$1,067,050
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	63
Median	60
Standard Deviation	7
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 proposal have the necessary significance and potential for impact?
Yes: 6	• There is a major bottleneck in the production of AAV and related viral vectors for first in human trials. This is especially true for indications with small patient populations, such as orphan diseases. The proposal describes the development of a novel small-scale bioreactor that enables the production of high titer viral vectors for therapeutic applications. If successful, this device would have a significant impact for many orphan diseases that have tremendous unmet medical need. • This device is being developed to enable the production of AAV for both in vivo gene therapy and for ex vivo gene engineering of hematopoietic stem cells (HSCs). This type of a product is likely to increase the success of developing stem cell technologies and therapeutics. The product will enable the rapid acceleration of manufacturing and development of multi-modality therapies, including AAV gene therapies and gene modified HSC therapies. • The concept is interesting, but lacked focus on how to move forward.
No: 7	• It is a conceptual project; it is not evident that a large scale AAV production can be achieved using the proposed strategy. Thus, the impact is likely to be rather small. • Needs additional data to support the proposal and feasibility of the approach. • While there are AAV bottlenecks for their manufacture, the described product is unlikely to impact this unmet medical need due to lack of scalability of the technology. Membrane technologies with high oxygenation will unlikely be scaled beyond the small scale, limiting the applicability of this technology. • The product is at a conceptual stage and there is no significant data to suggest that the technology will provide sufficient value. I would like to see evidence that the technology can be scaled up.
GWG Votes	**Is the rationale sound?**
Yes: 6	• Superproduction of AAV, using the system, is achieved by combining a proprietary high density cell respirator (HDCR) bioreactor with their custom producer cell lines. The scientific and technical rationale for the device is built on a sound foundation of bioprocess and viral vector manufacturing principles. • The rationale appears to be sound. • The rationale is there but lacked sufficient preliminary data. • The preliminary data support additional development of the product. However, the project and proposal need to be modified to enable a more clear and well-defined line of sight toward clinical and therapeutic application. • The preliminary data is convincing proof of concept that the team is capable of producing vector that is effective and potent for in vivo gene therapy applications. However, it is unclear if this vector will be sufficient for HSC or stem cell gene engineering efforts. There is not preliminary data for that type of application. • Figure 3 is not completely accurate. The higher cost at a contract development and manufacturing company is often driven by the higher cost of goods for "GMP grade" starting materials, Quality Systems, Operators, QC, etc.…which are very different from the research stage. How much of this cost difference is truly due to manufacturing efficiency vs different infrastructure needs? What would be the true cost to make AAV using the HDCR approach in a cGMP environment compared to the standard benchmark?
No: 7	• Increased oxygenation has been shown to increase the density of cells, but there are other methods that are more scalable that can accomplish the same effect. There is a reason bio-manufacturing has gravitated towards single use tank bioreactors - they are scalable, which is essential for large scale vector manufacturing. • There is limited data to support the proposition. Also, I only found an abstract and no publication on the technology. The increase in titer in Figure 6 seems to be direct result of increased density using a non-scalable technology. • The data is very limited and not sufficient to support development of the product.
GWG Votes	**Is the proposal well planned and designed?**
Yes:	*none*

0	
No: 13	• The program and concept are compelling. There are some gaps in the overall program that need to be addressed to make this a stronger application. • All preliminary data in this grant has been generated within the context of in vivo AAV gene therapy encoding reporter transgenes. Is the vector produced by the process of sufficient quality to enable gene editing in an HSC? High multiplicity of infection and quality have been major bottlenecks. Is there any proof of concept for non-reporter genes of interest? What is the plan around development and process optimization of the platform using constructs that are therapeutically and clinical relevant? • Needs more preliminary data and planning of the approach. Needs more process development focus. • While the tool could apply to several different areas, the plan for the next 24 months lacked clarity regarding how to get to a place where the tool would be ready for commercial manufacturing. • The plan is not well thought through. In specific Aim 1.2, for example, the goal is to compare linearized plasmid, transposon, and lentiviral integration approaches for the generation of the packaging cell line. There is no thought to regulatory considerations here. It would be highly unlikely that the FDA would approve a packaging cell line for AAV production with resident lentiviral vector sequences in the cell line. • The proposal is constructed around developing packaging cell lines without any specific aims devoted to scale-up, process development of supposedly highly concentrated vector is completely missing and the lack of generation of GMP master cell banks for GMP AAV production and any of the quality systems needed to support such a product casts considerable cloud on this program. • The proposal lacks description of many technical details. No plans for downstream development of the technology are presented, no scale up or system validation plans are described. Plans for regulatory support are not provided. • The application focuses on cell line development without consideration of all the other aspects for producing a GMP cell line. The manufacturing and quality systems needed for its utility are completely absent from this application.
GWG Votes	**Is the proposal feasible?**
Yes: 5	• There is a partnership with a respected investigator in the field. The other staff appear to be qualified to perform the tasks in the proposal. • The proposal is feasible, but for small, not large-scale production of AAV. • The team seems to lack regulatory and data/IT support. Given that this is being developed as a manufacturing bioreactor/device for use in the cGMP environment, it'll be important for the team to build out capabilities that enable deployment of the device in a regulated cGMP environment. It is unclear if the team actually has this capability. • The contingency plans seem fairly superficial. They don't, for example, take into consideration of regulatory and quality risks associated with developing a bioreactor for the cGMP environment. It would be good for the team to more fully flesh out the contingency plans.
No: 8	• The plan can be more clearly defined, including relating to how they intend to transition to manufacturing for commercialization. • It was not clearly explained how the performance targets were selected, and what might impact reaching those targets. • There is a need for teams to provide quality and regulatory support.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 6	• If successful, this gene therapy foundry can benefit different patient populations, including an underserved community.
No: 7	• While the tool may have a wide range of uses, the application lacked detail about how underserved communities could be specifically helped. • Additional clarity would be useful regarding how this product may aid underserved communities. • Developing low cost vector manufacturing processes does address health equity issues. However, the plan is not sufficiently developed to be able to actualize it.

Application #	TRAN1-13314
Title (as written by the applicant)	An Ocular Gene Therapy to Treat Dry Age-related Macular Degeneration (AMD) - An Unmet Need
Translational Candidate (as written by the applicant)	An ocular gene therapy to renew retinal stem cells, improve vision, and prevent blindness from dry age-related macular degeneration (AMD).
Area of Impact (as written by the applicant)	The targeted area of impact is the development of a novel modifier gene therapy to rejuvenate retinal cells and prevent vision loss due to AMD.
Mechanism of Action (as written by the applicant)	The proposed candidate activates multiple cell survival pathways in the retina and the retinal pigment epithelium to prevent oxidative stress induced damage. This gene therapy: 1) Increases retinal stem cell gene expression, 2) Increases antioxidant enzymes, 3) Prevents programmed cell death, 4) Reduces DNA damage, and 5) Regulates the complement pathway Simultaneous activation of these pathways in a combined manner prevents retinal death and preserves retinal function.
Unmet Medical Need (as written by the applicant)	Dry macular degeneration is the leading cause of vision loss in the elderly with no current available treatment
Project Objective (as written by the applicant)	Clinical Good Manufacturing Practices (cGMP) manufacturing readiness and pre-IND meeting.
Major Proposed Activities (as written by the applicant)	• Determine target dose range and demonstrate 3-month safety/toxicity in a mini pig animal model. • Obtain 12-month safety, toxicity, biodistribution, and immunogenicity data after administering gene therapy in a mini pig animal model. • Scale-up research grade gene therapy manufacturing to cGMP manufacturing with production quality standards suitable for intraocular use.
Statement of Benefit to California (as written by the applicant)	Age-related macular degeneration is a condition where the retina is damaged leading to progressive irreversible vision loss, and there is no current therapy available. AMD affects 1.3 million Californians today and the number is expected to double by 2050 due to the aging population. The annual economic impact on the California economy is $8B (NEI data). Developing an effective preventative therapy would improve Californian welfare and reduce the economic burden of low vision-associated disability.
Funds Requested	$3,197,261
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: --

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

Mean	--
Median	--
Standard Deviation	--
Highest	--
Lowest	--

Count	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 proposal have the necessary significance and potential for impact?
Yes: 6	• Currently there are no good treatment options for Age-related Macular Degeneration (AMD). This proposal aims to address this unmet medical need. • The proposal is significant and if successful, will address an unmet clinical need. • The proposed study does have the necessary significance and potential for impact.
No: 7	• This will be high-impact if it works, as there are 1.3 million Californians with early-stage AMD. • Other therapies in development include cellular products administered directly into the eye to repopulate the retinal pigment epithelial (RPE) cell layer, though none of these cell therapies has completed clinical development. There are also other AAV gene therapies in development for this condition. • Repopulation of the retinal pigment epithelial (RPE) cell layer, if successful, has the potential to prevent degeneration in the overlying photoreceptor layer and vision loss in dry AMD. This therapy might overcome some of the limitations that have been observed for cell-based therapy for dry AMD. However, it is not clear why selection of the gene BMi1 is expected to be more successful than previously attempted gene therapies for dry AMD. • There is currently no treatment for dry AMD. The proposed AAV-BLMi1 gene therapy, if successful, would address an unmet medical need. However, limitations in the supporting data and study design raise concerns as to whether this will have the therapeutic benefits the applicants anticipate.
GWG Votes	**Is the rationale sound?**
Yes: 0	*none*
No: 13	• That Bmi1 plays a key role in retinal development and homeostasis is well-supported, but its potential role and use as a therapeutic target in dry AMD is not. A major concern is that no evidence is provided to demonstrate (a) a link between dry AMD and changes in Bmi1 levels in the retina or (b) that Bmi1 downregulation results in a dry AMD-like phenotype. The application should at least include preliminary data showing Bmi1 levels in healthy versus dry AMD eyes. • The existing efficacy data are not adequate. The first efficacy study uses young mice treated 6 weeks before retinal damage was induced. In the second efficacy study, the treatment and injury were administered at the same time in non-aged mice. A better approach to showing preclinical proof-of-concept is needed. • Clinically, invasive gene therapy for dry AMD will most likely not occur until mid-stage disease. Thus it would be more appropriate for the investigators to assess neuroprotection by administering gene therapy following injury. • The supporting data presented do not provide confidence that a product will be generated since (a) gene therapy in the translational studies was performed either 6 weeks prior to, or immediately upon, retinal damage which will not equate to the clinical scenario where treatment of this kind will most likely be performed at mid stage dry AMD; (b) the applicants have used two acute retinal damage models which do not reflect the chronic pathogenesis of dry AMD; and (c) an intravitreal approach might be preferable to the more invasive and problematic subretinal route. • The authors propose a potency assay using Bmi1 transgene expression after transduction of cultured primary cells. The use of primary cells may be impractical for measuring the potency of the clinical or commercial product. AMD-relevant cell lines (if there are any) should be validated. • There is no strong evidence that Bmi1 represents a promising gene therapy target for preservation of the retina in AMD.

	• There is insufficient evidence that BMI1 is the proper target for this therapy. • The authors did not provide data to support a clear link between Bmi1 expression level and AMD pathogenesis. The role of Bmi1 in retinal progenitor cells is not specific.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 2	• It will be good to have a pre-pre-IND (INTERACT) meeting with FDA to get feedback on animal studies.
No: 11	• The potential efficacy of the proposed approach is not adequately demonstrated. The proposed animal models are acute injury models and do not mimic AMD well. The proposed route of Bmi1 delivery might not be optimal. The proposal has several other technical issues. • Proof-of-concept studies showing a treatment, rather than preventative, effect are needed. • In the proposed pig dose-range study, the target is a 50% increase in retinal Bmi1 levels and a 2-fold increase in RPE Bm1 levels, which is based on data from normal rodents. The rationale for these targets is not clear. How do they these targets translate to potential efficacy in older patients with macular degeneration? • A major concern is that the data from the Pharmacology, Biodistribution and Pharmacokinetics section will not be robust given the small number of animals proposed, along with the multiple doses and timepoints to be tested. These limit any meaningful statistical analyses. Furthermore, these are relatively young animals without pathology and pharmacokinetics may be very different in older animals with a compromised retina. It also appears that some of the techniques to be used have not been developed. • Animal numbers and statistical significance are problematic in the Pilot Safety Study design. • Accurate retinal electrophysiology is challenging and requires direct expertise, which I don't see on the applicant team. • The Regulatory and Clinical Strategy section needs more detail. • Based on limitations in the preliminary data and project plan, applicants do not seem to be on the path to a pre-IND meeting with the FDA.
GWG Votes	**Is the proposal feasible?**
Yes: 5	• Appropriate consultants and contractors have been identified to conduct the planned studies. • Timeline and budget contingencies are mentioned in the application, but I don't see mitigation plans for risks such as a lack of dose response or demonstrated efficacy in the animal studies. • The project appears feasible to conduct. There are several contractors and consultants involved. Overall, with outsourcing, the team appears qualified to perform the work.
No: 8	• The feasibility of the proposed work is compromised by technical issues. • The potential tumorigenicity of Bmi1 overexpression is not sufficiently addressed. • Insufficient attention to safety concerns associated with the upregulation of BMI1. • The proposed milestones are realistic and can be achieved within the proposed timeline. However, the applicant team's experience and expertise in gene therapy, eye research, AMD, and pig studies is more limited than I would hope to see for this project. • The team should include a statistician as a Key Person to increase the rigor in the project plans. • The contractor research organizations named in the application all have the ability to perform the contracted studies. However, I notice that some of the cost quotes do not match the studies in the project plan. • Alternative approaches are not adequately addressed.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 9	• The applicant is responsive to the needs of underserved communities and their approach to inclusivity is robust. • The applicant company plans to appoint an outreach team to ensure diversity, equity, and inclusion (DEI) and access for underrepresented Californians. They will partner with several service organizations including a clinic that provides free eye care to underserved populations in California. • The applicants have considered the needs of underserved communities in their application. • The project plans show consideration of underserved communities.
No: 4	*none*