Application #	CLIN2-15282 #2
Title (as written by the applicant)	RPESC-RPE Therapy for dry Age-related Macular Degeneration
Therapeutic Candidate (as written by the applicant)	Retina pigment epithelial stem cell (RPESC)-derived RPE progeny (RPESC-RPE)
Indication (as written by the applicant)	Dry age-related macular degeneration (dry AMD).
Unmet Medical Need (as written by the applicant)	Many people experience vision loss due to dry AMD and there is no current therapy to improve vision. Transplantation of RPESC-RPE cells aims to restore vision that has been lost to dry AMD disease progression.
Major Proposed Activities (as written by the applicant)	• Clinical sites for the ongoing trial will be opened in California. • Manufacturing of RPESC-RPE-4W cell product in California.
Statement of Benefit to California (as written by the applicant)	Many Californians with vision loss due to dry AMD lack available vision-improving treatment option. Development of a treatment to improve vision lost to dry AMD will enable tasks of everyday living. To restore dry AMD patient ability to travel, work and play.
Funds Requested	$4,009,675
GWG Recommendation	**Tier 1: warrants 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: 1

Up to 15 scientific members of the GWG score each application. The final score for an application is the majority score of all of the individual member scores. If there is no majority score, the final score is 2. Additional parameters related to the score are shown below.

Highest	1
Lowest	1
Count	15
Votes for Tier 1	15
Votes for Tier 2	0
Votes for Tier 3	0

A score of "1" means that the application has exceptional merit and warrants funding.

- A score of "2" means that the application needs improvement and does not warrant funding at this time but could be resubmitted to address areas for improvement.
- A score of "3" means that the application is sufficiently flawed that it does not warrant funding.

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 14 **No:** 0	• There is a very large unmet need for treating and slowing down geographic atrophy progression and visual acuity from dry AMD. Several treatments have been approved but require repeat intra-vitreal injections with associated risks, and only slow down progression; they do not bring back sight. The currently approved Iveric compound even increases conversion to wet AMD. • The applicant has developed a cell therapy from adult RPESC with preclinical efficacy studies showing that RPESC-RPE cells at an intermediate progenitor stage are most effective at engraftment and vision rescue. The ongoing phase 1/2a clinical trial in dry AMD is demonstrating encouraging preliminary results. Thus, this cell therapy has the potential of improving vision in patients with dry AMD rather than solely slowing progression as with the current SOC treatment. • This treatment offers an exciting potential therapy for a large unmet need in retinal disease. • The candidate product appears to improve vision which would be a game changer. • This is a very exciting proposal to add two California clinical retinal sites for an ongoing phase 1/2a that in four patients has shown incredible, life changing efficacy. • Improvement in visual acuity is an aspirational goal that has the potential for significant benefit. • The product candidate will 100% provide an improvement over standard of care, if successful. Although there are a lot of cell transplants, small molecules and biologics in development, nothing has been shown to improve and restore vision. This preliminary data in four patients can be game changing. • This therapy, short of the surgical delivery procedure (single event) and risks of 6 months of immunosuppression, can be game changing. • The candidate product offers a sufficient value proposition to be adopted by patients and health care payers, given the cGMP and proposed costs of goods (COGs). • The addition of the visual acuity in the contralateral eyes have reinforced the value and potential of this investigative therapy along with the safety profile, makes it exciting and a real potential. • The resubmission improves the initial submission for a product that will treat geographic atrophy. There are two approved therapies; however, there is an unmet medical need for a better therapy based on a different mechanism of action. • The proposed project addresses a clear unmet medical need to treat geographic atrophy. There are two newly approved therapies for GA, but neither reverse the visual loss.
GWG Votes	**Is the rationale sound?**
Yes: 14 **No:** 0	• The rationale is very sound. Numerous RPE based transplants, embryonic and pluripotent, should have proof of mechanism and proof of concept, but have fallen short. This idea of allogeneic adult RPE-SC with the potential to proliferate and then be redelivered is brilliant. • The ongoing phase 1/2a has been de-risked from a regulatory and preclinical perspective. Now the team have data with impressive visual acuity gains, no serious adverse events, and maintained visual acuity improvements even after immunosuppression has been stopped at six months. • The PI has addressed the concerns and queries of the prior CIRM review. • In the revised application, the applicant provided additional clinical data from the first 4 subjects. Three subjects had a clinically meaningful gain of visual acuity after a six-month period without immune suppression. These additional clinical data strengthen the rationale and support the continuation of this phase 1/2a study. • Encouraging safety profile and improvements in visual acuity are reported in three patients. Hence, there is enough enthusiasm to see how the trial develops once more patients are treated and more detailed data is available on safety and efficacy. • Prior therapies slow progression but do not improve visual acuity. Encouraging clinical improvement is seen in the small trial. The goal of the CLIN2 award is to increase manufacturing capacity and to expand the trial into California sites. • The phase 1/2a trial has been de-risked to a significant degree. • The rationale is based on nonclinical and clinical data collected to date. • Their rationale and preclinical safety profile is now being validated in humans. The data support continued development. • They are mindful of evaluating repeat surgical implantation and cryopreserved (cGMP) RPE cell lines to scale up their process for future clinical development. • It is not unusual in ophthalmology to see a discordance between structure and function endpoints. The fact the better seeing individual had such high visual acuity gains may speak to the fact that there are still more viable cells and retinal structure to function.

GWG Votes	Is the project well planned and designed?
Yes: 14 **No:** 0	• The proposal presents a thorough approach, reasonable endpoints which were pre- discussed with FDA, and sound manufacturing. • The cGMP plan is reasonable, doable and necessary. The team has had extensive communications with the FDA. The designs, processes and COGs seem very reasonable for scalability. • This treatment offers exciting potential; the safety profile is good. • The resubmission clarifies some of the plans for the program with improvements to the design of the clinical trial. • The phase 1/2a protocol has been revised to clarify that the timing of assessment for the primary endpoint will be assessed at Month 12. The additional assessments through Month 24 are considered long-term follow-up. • The applicant has now provided a possible explanation for the apparent mismatch between improvements in certain endpoints. • They have sorted out the issues from the prior review and addressed the slower recruitment based on strict visual acuity inclusion and exclusion criteria. Having a site in California which is active fostering DEI in clinical research work should help recruitment. • This initial study is necessary for dose selection, initial safety, and expansion of clinical sites. Together with cGMP CMC plans, this project can enable more rapid clinical development and NDA submission. • Although an amendment to the protocol was provided with the resubmission, no list of changes or redline version of the protocol were provided. The revised protocol does not appear to include a description of how visual acuity measurements are obtained, including the addition of a second assessor that is described in the revised application. As this is a multi-site study, a reviewer recommends including detailed descriptions of study assessments in the protocol or an ancillary study document to reduce site-to-site variation.
GWG Votes	**Is the project feasible?**
Yes: 14 **No:** 0	• The objectives are feasible and proposed timeline reasonable. The fact that four patients on average have gained clinically significant visual acuity improvements in one month that stabilized out past six months is incredible. • Given the ongoing clinical trial, the program is feasible. • They have addressed the prior slow recruitment. • The applicant presents a revised timeline and encouraging revised recruitment plans. Appropriate expertise is on the team. • The team has been working with FDA and has a viable plan for derisking the asset and product. • In the resubmission, the applicant has provided an explanation for the initial slow enrollment as being due to inclusion criteria and logistical challenges. Apparently both issues have been addressed; however, the additional CA sites are needed to increase the enrollment rate. • The proposed team is appropriately qualified and staffed. They have access to all the necessary resources to conduct the proposed activities, including manufacturing. They are working with top notch vendors, clinicians and CROs.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 14 **No:** 0	• The team has put together a very nice summary of how they will work to accomplish and meet their DEI goals. • Applicants provide an appropriate DEI plan. • The proposal appears appropriate for the stage of clinical development and the expected affected populations. • The protocol has been revised so that expenses are now fully reimbursable. • In the revised trial population table, the percentages in the Population Goal column seem to be incorrect as these should total up to 100%.

DIVERSITY, EQUITY, AND INCLUSION IN RESEARCH

Following the panel's discussion of the application, the patient advocate and nurse members of the GWG were asked to indicate whether the application addressed diversity, equity and inclusion, and to provide brief comments. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

DEI Score: 8

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

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	0	*None*
6-8: Responsive	5	• DEI response is very good. • The applicant provided demographic data despite surprising reduced availability of broad scale data sets. A 2022 publication informs goals for trial participation targets. Two studies cited highlight the correlation of AMD with poverty. • Importantly, there is good acknowledgment of challenges and factors with respect to trial participation engendered by visual impairment that are unique to that patient population. As such, the applicants plan to remind the study investigators that age, sex, race, ethnicity, family income, and health insurance correlate with visual difficulty. Study investigators will be asked to advise trial staff that inequities increase the incidence of blinding disease. As such, the team state that including demographic subgroup analysis is important, and recruitment from underserved populations is critical to serve the trial's goals. • Recruitment into the trial aims to include individuals of diverse race, ethnicity, sex, and gender. Proactive recruitment of underserved groups will be undertaken through outreach to inform community clinics and associations for the blind that provide care to the underserved. This community outreach will promote enrollment that includes underserved demographic groups. Specific clinical sites, including a CIRM alpha clinic, will be of substantial aid in supporting those efforts with their track record and patient pool. Given the experience of the PI, there are good community outreach plans. • The applicant will engage resource centers for the blind and visually impaired who mainly serve poor, multi-handicapped and ethnically diverse populations as substantiated by a panelist familiar with these institutions. • Budget is being made available for travel, lodging meals and lost wages to reduce the impact of participation. The first approximately ten patients will all be at a California university which has an outstanding track record in patient DEI participation.
3-5: Not fully responsive	0	*None*
0-2: Not responsive	0	*None*

Application #	CLIN2-15311
Title (as written by the applicant)	A Phase I/IIa Study to Evaluate the Efficacy of a Gene Therapy with Standard of Care Therapy in Newly Diagnosed High Grade Glioma
Therapeutic Candidate (as written by the applicant)	A retroviral replicating vector expressing yeast cytosine deaminase, which converts an antifungal prodrug to an anticancer drug
Indication (as written by the applicant)	Newly diagnosed high-grade glioma
Unmet Medical Need (as written by the applicant)	Malignant gliomas account for 70% of primary brain tumors. Standard of care consisting of resection, radiation and temozolomide results in a progression free survival of 6.9 months and overall survival of 14.6 months. Overall prognosis for this disease remains poor and remains a critical unmet need.
Major Proposed Activities (as written by the applicant)	• Clinical trial initiation and implementation • Correlative research studies
Statement of Benefit to California (as written by the applicant)	This first-in-human clinical trial will evaluate the safety and efficacy of a novel gene therapy technology in newly diagnosed high-grade glioma patients. This trial will be conducted at three institutions in California. The Investigational Product was spun out of two California institutions, and a candidate biomarker has been identified by a California based company.
Funds Requested	$11,807,220
GWG Recommendation	**Tier 1: warrants 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: 1

Up to 15 scientific members of the GWG score each application. The final score for an application is the majority score of all of the individual member scores. If there is no majority score, the final score is 2. Additional parameters related to the score are shown below.

Highest	1
Lowest	1
Count	15
Votes for Tier 1	15
Votes for Tier 2	0
Votes for Tier 3	0

- A score of “1” means that the application has exceptional merit and warrants funding.
- A score of “2” means that the application needs improvement and does not warrant funding at this time but could be resubmitted to address areas for improvement.
- A score of “3” means that the application is sufficiently flawed that it does not warrant funding.

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 14 **No:** 0	• The proposal addresses an unmet medical need in that the target indication is high-grade gliomas (HGG), a disease with a poor prognosis. • There is a critical need for new therapeutics for high-grade gliomas, which have a high mortality and morbidity. • The project holds potential significance for glioblastoma which has an unmet need. Data is impressive from another trial but with small numbers. • There is a high unmet need. • The project proposes a therapy which would meet an unmet medical need for the treatment of glioblastoma. Considering the ongoing clinical experience from the group and the categorical tumor-selective gene delivery, the proposed approach is likely to provide a sufficient value proposition that supports its adoption by health care providers. • The value proposition for this therapy partly comes from the replicative aspect of the product allowing for consistent production while being developed as a non-lytic replication agent. • The approach is likely to provide an improvement over the standard of care due to the nature of the product, following dosing, providing subsequent progeny cancer cells which become virus producer cells to further retroviral replication in a highly tumor-selective manner. • Pediatric patients with HGG may benefit if the proposed therapy is successful in adults.
GWG Votes	**Is the rationale sound?**
Yes: 14 **No:** 0	• The proposed project has a sound rationale. Ongoing clinical trials of prodrug activator gene therapy showed evidence of increased survival including tumor regression and disappearance of tumors. • The increased survival for the high-dose cohort has a median overall survival of over one year, as well as radiographic evidence of objective responses which support the continued development of the treatment at this stage. • A post-hoc analysis of data with the same product indicates a specific patient population defined by a biomarker. Only human clinical data will determine if this hypothesis will be supported. • The biomarker is exciting, but it is unclear what it is. Some background here would be nice.
GWG Votes	**Is the project well planned and designed?**
Yes: 14 **No:** 0	• The intended objectives for supplying a trial with a material available to be consistently manufactured is in place for the proposed product and its continued development. • The CMC studies proposed in the project plan are essential to continue the clinical development of the product. At its current state, stability testing costs were projected based on multiple GMP contract research organizations and the updated stability assurance costs are reasonable given industry standards for this type of drug product. • Manufacturing process is validated. • The biomarker results may be a benefit in determining the optimal regimen for specific subpopulations of patients.
GWG Votes	**Is the project feasible?**
Yes: 14 **No:** 0	• Given the product profile, including the progress to date with regards to the available clinical drug product lot, the applicant goals are likely to be achieved within the proposed timeline. • Manufacturing contingencies are available if needed. However, there is no current expectation for another lot of material to be generated to continue clinical development. The facility is established with the applicant's program allowing for the necessary resources to conduct a viable contingency plan to manage any material associated risks or delays. • The proposal outlines a feasible plan for treating and assessing patients in a complex regimen.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13	• An appropriate rationale for the study population is based on current knowledge of the demographic groups at risk. • With participating clinical trial sites that embrace DEI principles, the three named California trial sites will serve as referral centers for a majority of the patient population in CA. Also, the

No: 0	participating sites were selected based on their past experience with the product and recruitment. ● The proposal addresses key barriers to trial participation; clinical sites will provide translation and social support services to aid diagnosed patients. ● The project plan for trial engagement includes providing study physicians and coordinators with DEI training as a part of the site initiation visit. ● The data on biomarker prevalence may be useful in defining underserved populations that may be eligible for the product.

DIVERSITY, EQUITY, AND INCLUSION IN RESEARCH

Following the panel's discussion of the application, the patient advocate and nurse members of the GWG were asked to indicate whether the application addressed diversity, equity and inclusion, and to provide brief comments. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

DEI Score: 8

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

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	0	*None*
6-8: Responsive	5	● Great track record of broad scale patient participation. ● Strong DEI plan.
3-5: Not fully responsive	0	*None*
0-2: Not responsive	0	*None*

Application #	CLIN2-15343 #2
Title (as written by the applicant)	A PHASE 1B STUDY EVALUATING THE SAFETY AND EFFICACY OF AN ALLOGENEIC CELL THERAPY IN SUBJECTS WITH CLEAR CELL RENAL CELL CARCINOMA (ccRCC)
Therapeutic Candidate (as written by the applicant)	An allogeneic anti-CD70 CAR-T cell product will be evaluated for the treatment of advanced or metastatic clear cell renal cell carcinoma (ccRCC).
Indication (as written by the applicant)	Advanced or metastatic clear cell renal cell carcinoma (ccRCC)
Unmet Medical Need (as written by the applicant)	For patients with the most common kidney cancer globally, metastatic RCC, there are no approved treatments after second line TKI/ICI. Allogeneic CAR T cells that target CD70 positive cancer cells shows promising response rates and shorter time to initiation of treatment.
Major Proposed Activities (as written by the applicant)	• Manufacture product to supply the proposed trial • Assess safety, tolerability, and preliminary efficacy of the allogeneic product at Phase 1b expansion cohort dose regimen • Determine the recommended phase 2 regimen (RP2R)
Statement of Benefit to California (as written by the applicant)	The company is in a unique position to deliver transformative allogeneic CAR-T treatment to Californians and the world due our understanding of the product, manufacturing capabilities, and proven track record of delivering CAR-T cellular therapy since 2019. We have a state-of-the-art manufacturing facility in California, that is capable of producing life-saving products that will help the people in the state and the world.
Funds Requested	$15,000,000
GWG Recommendation	**Tier 1: warrants 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: 1

Up to 15 scientific members of the GWG score each application. The final score for an application is the majority score of all of the individual member scores. If there is no majority score, the final score is 2. Additional parameters related to the score are shown below.

Highest	1
Lowest	1
Count	14
Votes for Tier 1	14
Votes for Tier 2	0
Votes for Tier 3	0

- A score of “1” means that the application has exceptional merit and warrants funding.
- A score of “2” means that the application needs improvement and does not warrant funding at this time but could be resubmitted to address areas for improvement.
- A score of “3” means that the application is sufficiently flawed that it does not warrant funding.

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 13 **No:** 0	• The product in the proposal is an allogeneic CAR T cell product targeting a marker for clear cell renal carcinoma (ccRCC). Effective therapies for this indication represent an area of unmet need. • This proposal offers an attractive expansion of CAR T cell therapy into a new application, and involves a number of interesting modifications that could make the therapy more effective. • There are several ongoing clinical trials to test CAR T for RCC. These utilize a variety of targets and CAR T strategies, and optimal approaches are unknown. It is not clear whether the proposed product can produce long-term responses, especially since it is likely that there will be immune-clearance of the cells. Therefore, the approach is not necessarily unique at a high level. • There are currently no standard-of-care treatments for advanced RCC. RCC is known to be responsive to immunotherapy, therefore, CAR T should have some efficacy. Early phase 1a data using this product suggest activity in patients. • The applicants have carefully addressed the individual comments made by the reviewers. They have provided additional information and have rewritten parts of the Manufacturing Section to provide the requested information.
GWG Votes	**Is the rationale sound?**
Yes: 13 **No:** 0	• The rationale for using immunotherapy to treat ccRCC is sound in that conventional therapies are ineffective in the disease. It also makes sense to use CAR T cells because of their success in hematological malignancies. To do so requires additional engineering of the cell product to overcome potential problems, such as the ability of solid tumors to avoid immune-based therapies and failure of effector cells to proliferate and provide continuing efficacy. • The phase 1a portion of the trial is ongoing and has enrolled 28 participants. Data are presented for 19 patients. There was a 30% overall response rate for patients with tumors that express target antigen, but progression free survival is low suggesting that durability will be an issue. • The overall schema of this particular CAR T construct has been tested in lymphoma by targeting CD19 and has shown early efficacy and safety that is comparable to autologous CAR T. However, the long-term impact of allo CAR T is limited in this setting, likely due to the lack of persistence of the cells. • The heterogeneous nature of expression of the target antigen may present a barrier in individual patients who may relapse with antigen negative disease. The phase 1b portion of the trial will determine this. • The nonclinical and clinical data provided support the rationale for development of the product. • There are concerns about persistence and ongoing immune suppression caused by the product
GWG Votes	**Is the project well planned and designed?**
Yes: 13 **No:** 0	• The proposal seeks to carry out additional production runs followed by a phase 1b study as a follow up to the phase 1a study. The results, both safety and efficacy-wise, support continued clinical studies. • The purpose of the phase 1b study is to determine protocol safety and development of the phase 2 regimen. The secondary objectives are to quantify the infiltration of CAR T cells into RCC tumors and to determine the cut-off for target antigen expression by the neoplasm. • Additional correlative studies will be undertaken that should be meaningful to further development of CAR T for solid tumors. • The timeline appears to be appropriate. • An extensive manufacturing plan is provided. • The relative impact to Californians appears to be low, as only two of the 17 proposed sites and 19% of current participants are from the state. There is a suggestion that an additional two Californian sites will be added, but no specific documentation as such is provided. • Concerns on the manufacturing section have been adequately addressed and the requested information has been provided.
GWG Votes	**Is the project feasible?**
Yes:	• The applicant did an excellent job of addressing previous concerns.

13 **No:** 0	• The applicants have addressed concerns on a point-by-point basis and have done so effectively for manufacturing issues. They have added the requested information on masking to prevent T-cell fratricide and provided the available data on potential efficacy and on infections. The manufacturing section has been extensively revised to provide the requested information. It provides considerable additional information on the process, the contract manufacturing organization, release testing, batch to batch comparison, the manufacturing facility and risks. • It appears that the tasks can be carried out, based on previous data and ongoing correspondence with the FDA. • The team includes the appropriate expertise. • The resources appear sufficient for the proposed studies. • The sponsor has provided timelines and budgets that will enable the feasibility of program.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12 **No:** 1	• There have been essentially no changes to the DEI section, apart from additional information on possible new sites. • It appears the sponsor is focused on enrolling underserved populations. • The DEI Plan is adequate. The applicant made no meaningful changes to the DEI plan. • The expected participation appears to be out of sync with the prevalence rate. White prevalence is 35%, yet the expected trial participation is 65%. Black prevalence is 5.74%, participation is 10%. • Applicant states that trial population goals have been carefully considered to balance the practical limitations of enrolling metastatic RCC patients with different races, ethnicities, gender, with the need to meet long-range data collection objectives during a phase 1b trial and beyond. Commitment to diversity and inclusivity in clinical trials remains steadfast, as they strive to ensure the safety and efficacy of their product. • The clinical sites participating in the study include institutions with diverse populations. Sites were selected previously based on ability to enroll into a phase I CAR T trial. • There is a heavy reliance on site DEI efforts. • Applicant proposes several grassroots efforts such as working with leading kidney cancer advocacy organizations and their regional affiliates to develop patient-education programs that can directly and indirectly address patient concerns, provide accurate information regarding this disease, and create a pathway to connect with investigational sites. • There is adequate description of efforts to build cultural sensitivity.

DIVERSITY, EQUITY, AND INCLUSION IN RESEARCH

Following the panel's discussion of the application, the patient advocate and nurse members of the GWG were asked to indicate whether the application addressed diversity, equity and inclusion, and to provide brief comments. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

DEI Score: 7

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

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	0	*None*
6-8: Responsive	5	Solid data and helping reduce barriers to participation.
3-5: Not fully responsive	0	*None*
0-2: Not responsive	0	*None*

Application #	CLIN1-14852
Title (as written by the applicant)	IND-enabling studies for a 2nd Generation Vaccine Targeting Glioblastoma
Therapeutic Candidate (as written by the applicant)	A vaccine that is designed to enhance the immune response against glioblastoma tumors expressing EGFRvIII.
Indication (as written by the applicant)	Patients who have a diagnosis of glioblastoma whose tumor has recurred and the tumor is known to be positive for EGFRvIII
Unmet Medical Need (as written by the applicant)	Glioblastoma is one of the most tragic tumors with an inexorable progression. After initial therapy, virtually all tumors return but no consensus exists for treatment as no therapy is consistently effective. As such, there is a major unmet need to develop a drug for recurrent glioblastoma.
Major Proposed Activities (as written by the applicant)	• To manufacture the drug under GMP conditions and confirm its safety. • To conduct extensive assays to confirm the activity of the drug and establish assays that will be informative for monitoring patients. • Obtain an IND from the FDA and formalize the clinical trial.
Statement of Benefit to California (as written by the applicant)	Glioblastoma has a very dire prognosis with only ~9% surviving 5 years. The incidence increases with age and those 65+ are the most affected. California has the highest population of 65+ in the US leaving a disproportionate impact on this state. An improvement in survival will lessen the personal and economic impact on Californians. If successful, our vaccine will also illustrate a new strategy for enhancing the effectiveness of vaccines that could be applicable to cancer or infectious disease.
Funds Requested	$4,367,348
GWG Recommendation	**Tier 3: sufficiently flawed, cannot be resubmitted for 6 months**
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: 3

Up to 15 scientific members of the GWG score each application. The final score for an application is the majority score of all of the individual member scores. If there is no majority score, the final score is 2. Additional parameters related to the score are shown below.

Highest	3
Lowest	3
Count	15
Votes for Tier 1	0
Votes for Tier 2	0
Votes for Tier 3	15

- A score of “1” means that the application has exceptional merit and warrants funding.
- A score of “2” means that the application needs improvement and does not warrant funding at this time but could be resubmitted to address areas for improvement.
- A score of “3” means that the application is sufficiently flawed that it does not warrant funding.

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 4 **No:** 8	• The project proposes a therapy which would meet an unmet medical need for the treatment of glioblastoma. Considering the previous experience from the group and direction of success, the proposed approach is likely to provide advancements from the current standards of care. • Overall the peptide-based vaccine approach should provide a significant value proposition relative to other more complicated gene therapeutic based approaches which have potential for larger development and production costs. • Glioblastoma remains an unmet medical need. There are, however, currently programs in development that are showing promise. • The applicant admits that is likely that the product may need to be combined with other therapeutic modalities to be effective. • Unclear if clinical response will be strong enough to have impact.
GWG Votes	**Is the rationale sound?**
Yes: 0 **No:** 12	• The proposal provides evidence from previous clinical experience with the earlier generation of the peptide conjugate which supports the clinical rationale for the improved construct. However, the case for the proposed peptide to target cancer stem cells (CSCs) needs more supporting data. • Animal data, including the materials used to manufacture product for nonclinical studies, does support continued evaluation of the candidate for development. Demonstration of the vaccine's impact on target cells is not clear and additional in vitro data would be helpful to support the product. • Tumor peptide vaccines targeting EGFRvIII have shown equivocal clinical activity. • EGF receptor targeting has been somewhat disappointing in glioblastoma. • Unclear if targeting EGFR with immunotherapy approaches will really have benefit in the brain. • The justification for single dose in toxicological study is unclear. • No evidence for targeting of CSCs.
GWG Votes	**Is the project well planned and designed?**
Yes: 2 **No:** 10	• The project is well planned overall with suitable timelines proposed for development and qualification of test methods and production of clinical grade animal toxicology material. • The FDA denied a pre-IND based on previous pre-IND for a similar product. No information was provided regarding recommendations from the previous program. • It is unclear what material is intended for use in the toxicology study; importantly if similar process will be used compared to the clinical process. • The rationale for the proposed tox study design was not provided, including dose and regimen to support proposed clinical protocol. • The proposed toxicology study is not sufficiently justified nor does the protocol that was provided make sense. Sacrifice is proposed for Groups 1 and 4 at day 11 (but there is no Group 4), a control only group is proposed for sacrifice on Day 39. Toxicokinetic studies are mentioned but no animals are included for this purpose. Pretest serum for antibodies not generally collected in mice. Days of scheduled sacrifice are not generally on the day of the last dose. • With the institution's mass spectrometry facility described as impractical for research or informing decisions, the applicant requests the purchase of a LC MS/MS as it would significantly accelerate studies. It is not clear from the proposal that the level of internal expertise available to operate and maintain the proposed equipment will support accelerated studies. • A detailed implementation plan for the installation and qualification of the mass spec would benefit the proposal. The personnel dedicated or expected to provide support for the equipment should be included. • The equipment purchase rationale is not adequately justified.
GWG Votes	**Is the project feasible?**

Yes: 8 **No:** 3	• The project timelines are feasible to achieve the projected year 2 filing of the IND application with the FDA. • The team is staffed appropriately to support the clinical aspects and the virtual manufacturing aspects of the product. The use of product testing vendors for analysis by mass spec provides expertise to support testing. However, due to the criticality of the test method for release and stability testing and prolonged turn-around time for test articles, the proposal's request for supporting equipment is understandable. It is not clear if expertise to support the equipment is available. The timelines for equipment implementation are also unclear, and the applicant does not indicate whether there will be cross-qualification of the equipment with the institutional facility. • There is a concern that relevant assays to measure activity will not be available for Phase I, which may make it difficult to justify advancing expeditiously with an active dose to Phase II. • There is concern regarding stability of product based on experience with the previous product. • There is some concern with achieving timelines.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 11 **No:** 1	• The applicant is relying on host institution catchment area, experience, and resources. • The applicant has developed specific goals to achieve inclusive distribution for their future clinical trial product by enhancing enrollment for the Black and Latino population to at least match the distribution observed in the region. • The proposal includes outreach and engagement by various approaches, one of which includes creating information portals for the prognosis and treatment community by building a website and mobile app that will inform patients about various options and facets of glioblastoma.

DIVERSITY, EQUITY, AND INCLUSION IN RESEARCH

Following the panel's discussion of the application, the patient advocate and nurse members of the GWG were asked to indicate whether the application addressed diversity, equity and inclusion, and to provide brief comments. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

DEI Score: 8.0

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

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	0	*none*
6-8: Responsive	4	• Part 1: Robust discussion of incidence and prevalence across target population ethnic communities. Trial population goals seem appropriate. • Part 2: Heavy reliance on the applicant institution for trial participation. • The institutional office of diversity in medical education offices hold annual forums on improving diversity in medical education and clinical trials. The PIs of this application will attend at least one of these forums to learn the barriers to minority enrollment and methods for increasing enrollment. • The applicant will develop a social media presence for the trial on such platforms as Twitter, Facebook, Tiktok and Instagram. • There are several patient advocacy groups for glioblastoma. Since the target population for the trial will be recurrent glioblastoma, patients will likely already be participating in these groups and hence these patient resources will be an excellent means to reach out to patients. • The applicant describes building a website and mobile app for patient information. • The applicant will identify the neurosurgeons and neuro-oncologists in the catchment area and increase awareness of the clinical trial

		especially since there is no standard of care for recurrent glioblastoma. • The applicant provides a good description of their plans to overcome barriers to participation. • Part 3: Robust discussion of the ways that the applicant institution fosters a DEI-oriented climate.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*