Application #	CLIN1-14770 #3
Title (as written by the applicant)	Autologous Gene Corrected Sinus Basal Cells to Treat Serious Cystic Fibrosis Sinus Disease
Therapeutic Candidate (as written by the applicant)	Gene corrected autologous sinus airway basal stem cells from patients with Cystic Fibrosis.
Indication (as written by the applicant)	The proposed studies provide an innovative stem cell based approach with gene correction to treat chronic sinusitis in CF.
Unmet Medical Need (as written by the applicant)	Small molecule modulators for CF cannot treat all patients. Previous attempts using viral and non-viral gene therapies have been unsuccessful. CRISPR/Cas9 genome editing enabling the precise correction of CF causing mutations in airway stem cells offers a durable autologous cell therapy to treat CF.
Major Proposed Activities (as written by the applicant)	• Develop process for Patient Scale Manufacturing Runs and complete three runs that meet release specifications • Completion of nonclinical feasibility, safety and biodistribution studies • Submit clinical protocol to IRB and file an IND with the FDA
Statement of Benefit to California (as written by the applicant)	Cystic Fibrosis (CF) is one of the most common genetic diseases in California. There is no curative therapy for CF and CF patients spend a lifetime focused on mitigating the symptoms of their disease. Moreover, the costs of treating a single CF patient are enormous. Thus, the benefit to California if this proposal is successful is that it would improve the lives of its citizens (both patients and family members) while simultaneously decreasing the societal costs associated with this disease.
Funds Requested	$6,000,000
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: 12 **No:** 0	• Serious sinus disease associated with cystic fibrosis is an unmet medical need for a disease where other therapies have made major improvements in morbidity and mortality in the past two decades. • The need for successful cystic fibrosis therapy remains almost two decades after the first indication of a gene therapy. • There remains unmet need for people living with CF who have mutations not amenable to corrector/modulator therapy or who are unable to tolerate the correctors/modulators. While CF sinus disease does not drive mortality it does affect quality of life and the concepts may be relevant for CF lower respiratory tract disease. • The target population of severe sinus disease has been revised. • The proposed approach offers the potential for significant improvement of the standard of care by providing a permanent cystic fibrosis transmembrane conductance regulator (CFTR) mutation agnostic gene correction strategy. • The proposed method offers not only improved care, but longer lasting effects than current strategies. This is exciting. • This is an improved application and responsive to previous critiques.
GWG Votes	**Is the rationale sound?**
Yes: 12 **No:** 0	• The scientific rationale is sound; additional data has been provided to support proof of concept. • I found the science to be solid and rational and strongly supported by preliminary data. • Nonclinical data suggest there may be improvement in sinus disease with the corrected cell therapy. • The gene corrected cell engraftment in mice has been quantified as "approx 90%" without further detail. • Cells expressing the genes in mice have been shown from one donor. • Open chromatin profile is unaffected by gene correction. • The issue about infected environment remains unaddressed by in vivo studies but ultimately will be addressed in patients. • It will be important for the investigators to note if gene corrected cells from every patient grow sufficiently for treatment to be undertaken and if not, then in which patients failure occurs and if there is a mechanism that can be identified. • The investigators have still not addressed the issue that several donors had slower rates of proliferation. While the summary figure suggested no statistically significant difference this raises questions of variability in response and may mean that higher doses are needed for some donors. This should be monitored in the future preclinical work and considered in the in vivo studies when deciding dose for the clinical trial.
GWG Votes	**Is the project well planned and designed?**
Yes: 12 **No:** 0	• This is a revised proposal. In my opinion, the investigators have carefully, comprehensively and successfully responded to previous concerns and the current document represents an outstanding and important plan. It was also encouraging to see some of the new data published in a high impact peer-reviewed journal. • There is a well-designed, staged approach to manufacture including use of both healthy donor cells and patient derived cells. • The applicant has addressed questions from the FDA and previous CIRM reviews concerning the delivery of the cellular therapy. • The proposed preclinical program adequately addresses the FDA responses to the pre-IND questions. • The applicant has responded to specific requests from the previous CIRM review on the nonclinical and clinical studies. • Plan to assess human cells by scRNA seq is incorporated and should help inform dose for clinical trial. • The rationale for rabbit bronchoalveolar lavage has been clarified in response. • The numbers of animals to be used in the rabbit studies have been clarified in response to reviewers but it would be important to understand a few more details. Regarding dose, will one animal/gender from each dose cohort be sacrificed at each time point? What happens with the "back up animals"? Will they have sinus surgery and what dose will be given? In some parts of the application there is mention made of animals transplanted with vehicle alone as controls but most sections mentioning the rabbit study refer to the control as being the contra-lateral sinus. This should all be clarified.
GWG	**Is the project feasible?**

Votes	
Yes: 12 **No:** 0	• The impressive team members represent four laboratories with unique and overlapping expertise in basic and clinical research related to translational activities in stem cells and to CF. • The investigators have significantly improved an already sound proposal. Important new data include evidence that genome editing appears not to result in significant undesired chromosomal rearrangements, the chromatin profile at the CFTR locus is preserved and corrected cells show no proliferative apparent disadvantage. Further, when associated with an appropriate scaffold, the modified/corrected cells differentiate into epithelial sheets with restored CFTR function, and these cells generate major airway epithelial cell types and CFTR is expressed only in the correct cells. • The program is technically feasible. • The low cell correction rate could be problematic if the subsequent gene corrected cells fail to grow. That said, the percent shown is better than zero percent CFTR expression.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12 **No:** 0	• Excellent. • The applicant has provided a plan that is appropriate for this stage of development for this therapy. • Further details of the responsibilities of the patient navigator have been provided to improve patient participation and ensure inclusion of a diverse population. • No concerns.

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: 9

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

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	3	• Excellent DEI plan. • Applicant has identified a population of CF patients have CFTR mutations that are not responsive to modulator therapies and are largely comprised of ethnic minorities. A successful project could make a positive impact to this population. • Trial population goal of 15 patients at the proposed trial site is well matched by CF occurrences in California based on ethnicity and/or race, sex and age from diverse backgrounds. The anticipated patient population goal is 20% Hispanic, 15% Asian, and 65% White, with an equal distribution of male and female patients and 90% in the 20+ age group. • To ensure diverse and inclusive clinical trial participation, the applicant plans to implement educational outreach programs with appropriately worded materials in multiple languages. The applicant also leverages partnerships to ensure participation from diverse backgrounds. • Plans to collaborate with Cystic Fibrosis Research Institute (CFRI) to advocate for the trial's benefits and raise awareness about cystic fibrosis in ethnic minorities. Will engage in various activities, including hosting webinars, providing routine outreach care, and establishing an advisory panel that will include patient advocates. Use of social media, newsletters and educational flyers will also be leveraged. • Telehealth will be offered to ensure patient access and minimize the need for travel. A dedicated Patient Navigator will work with clinicians to address language and cultural barriers and ensure the needs of trial participants are met. • The trial will provide subsidized housing and transportation, translation services, and other support services to remove socioeconomic barriers and ensure equitable participation for all eligible patients and their

		families. • Applicants team will have access to various applicant institutional training programs to promote cultural sensitivity as well as leaning on the institution's overall excellent DEI culture.
6-8: Responsive	0	*none*
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	CLIN1-15399 #3
Title (as written by the applicant)	Development of a therapeutic monoclonal antibody for the treatment of myocardial infarction and heart failure
Therapeutic Candidate (as written by the applicant)	Fully Humanized monoclonal antibody targeting human ectonucleotide pyrophosphatase/phosphodiesterase (ENPP1)
Indication (as written by the applicant)	Heart Disease: To prevent the development of heart failure after heart attacks
Unmet Medical Need (as written by the applicant)	Approximately 7 million people in the United States have heart failure (HF) and once a diagnosis of HF is made, approximately 50% survive 5 years. Heart attacks contribute between 40-70% of all cases of HF. The agent being developed will prevent the development of HF after heart attacks.
Major Proposed Activities (as written by the applicant)	• Manufacturing of biologic to support IND enabling studies • IND enabling GLP toxicity studies • GMP preparation and production of drug substance and product
Statement of Benefit to California (as written by the applicant)	Cardiovascular disease remains a leading cause of death in California and accounts for nearly one third of all deaths. The prevalence of heart disease is close to 25% in individuals above the age of 75 and 7% of individuals above the age of 65 suffer from heart failure. Heart attacks are the leading cause of heart failure and the therapeutic agent developed here will prevent the development of heart failure after heart attacks and be of immense benefit to Californians.
Funds Requested	$5,999,998
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

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

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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	• Acute myocardial infarction and subsequent ischemic heart disease remain the leading cause of death globally. The need for a therapy that halts the progression to heart failure post infarction is significant. • Heart failure and acute myocardial infarctions remain unmet medical needs in the US and around the world. • This is certainly a large unmet medical need, and the proposed mechanism of action is novel as far as I'm aware. Current standard of care does not address the major complications of fibrosis and cardiac repair. • The translation of a drug that could either enhance repair and/or decrease cardiac fibrosis would be a significant advancement over the current standard of care for patients currently being treated for heart failure. • The proposal aims to target fibrosis formation after myocardial infarction (MI) as well as myocyte survival using a monoclonal antibody that targets ENPP1. The applicants have evidence that ENPP1 enhances fibrosis after MI and the degree of fibrosis negatively impacts clinical outcomes. • A one-time treatment with a monoclonal antibody that positively impacts outcomes of MI would be of great value and I am sure it would be adopted by patients and health care providers if the current pre-clinical outcomes can be repeated in the clinic. • Importantly, the proposed single administration drug could be used with the standard of care, which should facilitate enrollment of clinical trials. • This is a much-improved application and very responsive to previous critiques. An interesting, novel therapy. • There are still remaining questions about the use of CIRM funds for a monoclonal antibody, but it is viewed more as a programmatic decision.
GWG Votes	**Is the rationale sound?**
Yes: 13 **No:** 0	• The investigators propose the use of a monoclonal antibody to ENPP1 that in mice they have shown reduces inflammation and fibrosis while theoretically improving myocyte survival. Delivery of this agent within 24 hours of acute MI is anticipated to be beneficial in reducing scar expansion post infarct. • The applicants present several lines of evidence to show that impacting ENPP1 function can positively impact fibrosis and myocyte survival after MI. This includes gene knockout data showing that the lack of ENPP1 in the heart correlates with decreased fibrosis and improved outcomes in rodent models of MI. • In addition, the mAb the applicants have developed was demonstrated to significantly inhibit fibrosis and increase myocyte survival in a ENPP1 humanized mouse model of MI. • Available preclinical in vitro and in vivo preclinical data support further development. The in vivo proof of concept data includes generation of conditional knock-out mice and a humanized ENPP1 mouse model. Pharmacokinetic studies were conducted in humanized mice. Initial safety has been evaluated in the humanized ENPP1 model. • The nonclinical data provide a plausible rationale for the therapy. • Safety concerns raised in the last review of this grant have been addressed by the addition of pre-clinical studies in large animals and rodents. • There are still some queries about mechanism, although the animal study should help. • Some emphasis on efficacy in the large animal study along with the toxicity studies is recommended. This would help to convince future funders to move this product into clinical trials.
GWG Votes	**Is the project well planned and designed?**
Yes: 13 **No:** 0	• The proposal has a well-planned development program. • The applicants have had a pre-IND meeting with useful feedback from the agency. The project plan aims to complete all definitive pre-clinical testing required to submit an IND. The applicants have closely followed feedback from FDA in designing their studies. • The project plan is based closely on FDA feedback, so the studies are essential and have the potential to advance CIRM's mission. • When the pre-clinical studies are completed and absent any negative safety concerns, the applicants will be in a position to file an IND and enter the clinic. • The applicant has taken on board the previous feedback and modified accordingly, including a large animal study being undertaken. • The design of the toxicity study has been optimized to support a first in human study, better aligns with the principles of the 3Rs (Replacement, Reduction and Refinement) for animal use, and is consistent with current International Conference on Harmonization (ICH) guidelines with respect to proposed highest dose.

	• The evaluation of the proposed number of animals/sex/group for the test article arms of the study is the standard number that has been considered appropriate to evaluate any treatment modality in large animals. • The resubmission addressed most concerns, but MI size prior to treatment was not addressed. However, I am encouraged by the number of animals used in each group which may have helped to eliminate some potential initial differences between groups. • The investigators will undertake the animal studies suggested by the reviewers to gain insight into the risk of rupture post-delivery of the mAb. They also have addressed concerns about obtaining consent within the first 24 hours and have incorporated reviewer suggestions regarding manufacturing assays. • There are no concerns with the manufacturing plan. While they are scaling to a large bioreactor the contract manufacturer has a lot of experience in scaling biologics. Apart from routine testing of the GLP and GMP mAb, the only notable studies they will need to do are stability studies at the concentration they intend to use in the clinic with the GMP product. • The timeline looks appropriate and is achievable but also is not padded so delays could occur. It strikes a balance between urgency and risk. • Increasing myocardial oxygen consumption and energetics to improve cardiac function is understandable, but where does the oxygen come from in a chronic ligation model? The large animal ischemia/reperfusion model will be a key next step; however, the small 'n' is not likely to provide a good efficacy readout.
GWG Votes	**Is the project feasible?**
Yes: 13 **No:** 0	• Barring unforeseen circumstances, I believe the project can be completed in the proposed timeline. • The project is now feasible based upon recently completed studies. • This is an excellent team and they have plans in place to successfully run this study. • The team is very qualified, and the contract manufacturer has a good track record. • Monoclonal antibody therapies have a well-developed manufacturing and control pathway. • The clinical protocol is feasible with regulatory agencies providing guidance on the clinical trials and endpoints necessary. • The feasibility concerns regarding informed consent have been addressed as have the toxicity study designed to address the potential risks associated with repeat dosing. • The contingency plans are reasonable and well thought out. From a manufacturing perspective the major issues are lot failure which they have accounted for as well as the availability of specific GMP manufacturing materials. These could impact the timeline, but they are not showstoppers.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13 **No:** 0	• The DEI section of the application has been completely rewritten incorporating the reviewers' suggestions and anticipating new concerns. It is vastly improved. • They have adequately addressed previous review concerns around community engagement and outreach. • The revised proposal reflects a better understanding and implementation of the principles of DEI. • Very responsive to the previous critiques. • The applicant has revised their strategy; it appears to uphold the principles of DEI.

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: 10.0

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Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	4	• Excellent DEI plan. • The applicants reference using their institution's DEI resources to augment the engagement and outreach efforts.

		• The applicants took the suggestions from the prior review and addressed them. Responsive to the criticisms and provided more details as to their specific plans vs. deferring to the contract organization. • A great addition is establishing a community advisory board which includes members of minority communities, community leaders, healthcare professional and health equity researchers. The applicant will also include members of the DEI leadership at the applicant institution. Activities include town hall meetings, focus groups, and listening sessions. • The applicant is developing a concrete plan for patient assistance re: transportation costs, childcare, etc... • The applicant plans to offer language assistance and culturally appropriate educational materials. • Consent will be in multiple languages and geared to 6th – 8th grade literacy. There will be culturally appropriate messaging for communicating that standard of care is not disrupted, and the drug was safe in previous phase 1 studies.
6-8: Responsive	0	*none*
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*