APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Resubmission	Previous CIRM Funding	Disease Indication	Product Type	Approach
TRAN1-12905	Development of novel chimeric antigen receptor (CAR) T cell therapy in patients with recurrent EGFRvIII+ glioblastoma	**$4,556,536**	**Y**	**95**	93	6	75	100	13	1	Y	N	Glioblastoma	Cell and gene therapy	An autologous CAR T cell therapy that targets multiple antigens on glioblastoma tumor cells
TRAN4-13022	Human induced Pluripotent Stem Cell (iPSC)-derived micro-heart muscles for high-throughput cardiac drug discovery	**$1,119,382**	**Y**	**90**	89	2	86	92	13	0	Y	Y	Heart disease	Screening tool	Miniaturized array of iPSC heart muscle for use in high-throughput drug discovery
TRAN1-12911	Mucopolysaccharidosis type II: Plasma cell delivery of iduronate sulfatase	**$3,994,676**	**Y**	**88**	88	6	75	95	11	2	N	N	Mucopolysaccharidosis type II	Cell and gene therapy	Autologous B cell therapy that produces iduronate 2-sulfatase (IDS), the enzyme deficient in MPS II patients
TRAN1-12895	Hematopoietic Stem Cell Gene Therapy for Immunodysregulation Polyendocrinopathy Enteropathy X-linked (IPEX) Syndrome	**$3,551,332**	**Y**	**86**	86	2	83	89	10	2	N	N	IPEX Syndrome	Cell and gene therapy	Autologous hematopoietic stem cells modified with a lentiviral vector to restore regulated FoxP3 expression
TRAN1-12890	Clinical translation of human embryonic stem cell-derived protein therapy that positively regulates the regenerative capacity of post-natal muscle for treating myotonic dystrophy type 1 (DM1)	**$3,906,376**	**Y**	**85**	85	1	85	87	12	0	N	Y	Skeletal muscle disorders	Biologic	A fusion protein therapy that stimulates endogenous muscle stem cells to restore muscle strength and function
TRAN1-12987	Chimeric Antigen Receptors (CAR) for the treatment of refractory pediatric B-cell acute lymphoblastic leukemia	**$3,330,801**	**Y**	**85**	85	2	80	90	11	3	N	N	Pediatric B cell leukemia	Cell and gene therapy	An autologous CAR-T cell therapy that selectively recognizes a B cell restricted antigen
TRAN1-12893	Targeting stromal progenitors to prevent the development of heart failure	**$4,841,428**	**Y**	**85**	84	5	75	90	9	6	Y	Y	Heart failure	Biologic	A monoclonal antibody therapy that targets ENPP1 to reduce inflammatory response and augment heart repair
TRAN1-12920	Development of a gene editing therapy for Duchenne muscular dystrophy	**$3,400,000**	**Y**	**85**	84	3	78	90	9	4	N	Y	Duchenne muscular dystrophy	Gene therapy	A gene therapy for DMD that permanently removes a hotspot region of patient mutations to restore dystrophin
TRAN1-13059	A human neural stem cell therapeutic candidate for the treatment of chronic cervical spinal cord injury	**$5,552,611**	**Y**	**85**	84	4	75	90	8	5	Y	Y	Spinal cord injury	Cell therapy	An allogeneic neural stem cell therapy to treat chronic cervical spinal cord injury
TRAN1-12891	Clinical Translation of Allogenic Regenerative Cell Therapy for White Matter Stroke and Vascular Dementia	**$5,925,602**	**Y**	**85**	84	3	80	88	7	7	Y	Y	White matter stroke	Cell therapy	An allogeneic glial progenitor cell therapy to promote axon growth and connections after stroke
TRAN1-12907	Investigational New Drug (IND)-enabling studies of a wearable therapeutic device for cardiac regeneration after myocardial infarction (MI)	**$3,923,191**	**N**	**83**	83	4	78	90	6*	7	N	N			
TRAN1-12889	Optogenetic therapy for treating retinitis pigmentosa and other inherited retinal degenerations	**$3,997,636**	**N**	**80**	82	3	80	90	4	9	N	N			
TRAN1-12919	Pre-Clinical Development of a Gene Corrected Autologous Airway Stem Cell Therapy to Treat Cystic Fibrosis Sinus Disease	**$5,667,733**	**N**	**80**	81	2	78	84	0	14	Y	Y			
TRAN1-13048	Off-the-Shelf Natural Killer (NK) Cells Derived from Umbilical Cord Blood Stem Cells to Treat COVID-19	**$5,838,284**	**N**	**80**	80	5	70	85	1	12	Y	Y			
TRAN1-12892	Targeting scar-forming progenitors with a novel small molecule to reduce surgical complications of total joint replacement surgeries	**$2,729,307**	**N**	**60**	59	7	50	70	0	14	N	Y			
TRAN1-13021	Exosomes to Facilitate Tissue Regeneration after Volumetric Muscle Loss	**$5,386,117**	**N**	**60**	58	6	50	70	0	13	Y	Y			

* Qualify for Minority Report

Application #	TRAN1-12905
Title	Development of novel chimeric antigen receptor (CAR) T cell therapy in patients with recurrent EGFRvIII+ glioblastoma
Translational Candidate (as written by the applicant)	Human T cells transduced with a viral vector encoding an EGFRvIII-primed two-antigen chimeric antigen receptor (CAR)
Area of Impact (as written by the applicant)	Glioblastoma, the most common malignant brain tumor.
Mechanism of Action (as written by the applicant)	In our proposed system, the first antigen EGFRvIII, which is expressed exclusively but heterogenenously on glioblastoma (GBM) cells, primes our virally transduced T cells to express a chimeric antigen receptor (CAR) that recognizes two GBM antigens, thereby eradicating intracranial GBM cells that express either of the two antigens. In our preliminary studies efficacy was durable and superior to conventional CAR T cell therapies. Treatment with our CAR T cell therapy was associated with excellent persistence (>100 days *in vivo*) and immune memory.
Unmet Medical Need (as written by the applicant)	Glioblastoma is the most common malignant primary brain tumor, affecting approximately three out of 100,000 individuals/year in the United States. Patients' prognosis remains poor even after surgical resection, radiation and chemotherapy, with a 100% recurrence rate and median overall survival of approximately 20 months.
Project Objective (as written by the applicant)	Successful submission of a Pre-Investigational New Drug (IND) package
Major Proposed Activities (as written by the applicant)	• Process development for manufacturing of CAR T cells • *In vivo* (rodent) studies to determine preclinical efficacy and safety of the proposed cell products • Development of the clinical trial protocol, consent form and clinical standard operating procedures
Statement of Benefit to California (as written by the applicant)	Because California's current population is nearly 40 million, approximately 1,200 people are likely to be diagnosed with glioblastoma every year. The tumor center at our institution is one of the most established brain tumor research and treatment centers in the world. Our scientists and health care clinicians work in partnership to translate laboratory findings into new or improved clinical therapies for patients in California.
Funds Requested	$4,556,536
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All Grants Working Group (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: 95

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

Mean	93
Median	95
Standard Deviation	6
Highest	100
Lowest	75
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	1

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 13	• The rationale for this work was considered sound by the reviewers of the first, funded submission. In this new submission the applicant has addressed the prior concerns provided by the review panel, and these changes further strengthen the proposal. • The proposal addresses an unmet medical need. This is a new submission for a CIRM-funded project. The authors are requesting additional funding for manufacturing. • The authors propose to develop a CAR T product for adults with EGFRvIII+ glioblastoma (GBM) whose disease has recurred/progressed after standard initial treatment, who have not received any prior therapy targeting EGFR, and for whom surgical de-bulking or biopsy is clinically indicated. This product will address a significant unmet medical need, as there are currently no curative therapies for GBM. • This product is not a traditional stem cell product. However, the applicants show that there is a detectable population of naïve/stem-like memory T cells in their CAR T drug product. If this product is clinically successful, it will increase the likelihood of successfully developing a stem cell technology that significantly improves patient care.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• In previous evaluations, the reviewers decided that the likelihood of success on this project and the need for developing new therapies for glioblastoma supported merit-based funding. This project is essentially an extension of the already-funded project. • GBM is a solid tumor with heterogenous expression of cell-surface targets. A multi-targeted therapy is likely the best approach for making a meaningful clinical impact in this indication. Within this context, the applicants propose to develop a multi-targeted CAR-T therapy that will target EGFRvIII. Upon activation, the EGFRvIII+ cells will express a CAR construct specific for antigens expressed on other GBM cells, thereby enhancing eradication of the GBM tumor. • The applicant has generated a robust body of pre-clinical data that support the overall development of the proposed product.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 13	• This project was already approved and funded for the development of a new CAR T cell therapy for glioblastoma. The applicant was advised by CIRM to resubmit the proposal with additional manufacturing needs included in the budget. • The possibility of success is such that this product may offer an impactful proposition for patients and healthcare providers. • Based on comments for their previous submission, the authors have gone back to the drawing board and proposed a less aggressive but more practically attainable timeline. This timeline continues to maintain the urgency associated with CIRM's mission. • The proposal is well planned.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 13	• The project is appropriately planned and designed, and has been strengthened with increased percent effort of the project manager and by the hiring a part-time medical writer to assist the development of the clinical protocol and the informed consent form. • Yes, this is a top-notch team. They are also partnering with key institutions in those areas where they lack the requisite expertise. • The proposal appears feasible.
No:	*none*

0	
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 13	• Glioblastoma is a problem that does not select for any particular ethnic group, and all patients would benefit from having improved therapy. • Yes, the applicant has done a good job on this front.
No: 0	*none*

Application #	TRAN4-13022
Title	Human induced Pluripotent Stem Cell (iPSC)-derived micro-heart muscles for high-throughput cardiac drug discovery
Translational Candidate (as written by the applicant)	*In vitro* miniaturized array of heart muscle amenable for use in efficient high-throughput drug discovery and screening campaigns.
Area of Impact (as written by the applicant)	Effective high-throughput screening of drugs on human heart muscles does not exist, hindering the discovery of therapeutics to treat heart failure.
Mechanism of Action (as written by the applicant)	Current approaches for drug discovery often miss a vast majority of druggable targets. Our approach for high throughput screening will provide a new platform for the more efficient drug discovery in human heart muscles exhibiting physiological features and drug responses, which cannot be achieved in two dimensional cardiac preparations. The proposed tool can be used in large-scale screening campaigns for *de novo* cardiovascular drug discovery or drug repurposing, at a reduced cost.
Unmet Medical Need (as written by the applicant)	Innovation in heart failure therapeutics is lacking, despite the severity of the disease. Current pharmacologic approaches are suboptimal, thus mortality associated to heart failure remains high. Developing a tool for high-throughput drug discovery will lead to improved pharmacologic treatments.
Project Objective (as written by the applicant)	High-throughput drug discovery and screening tool.
Major Proposed Activities (as written by the applicant)	• Fabrication of the high-throughput screening tool to identify drugs to treat heart disease • Validate the heart muscle platform with an Food and Drug Administration (FDA)-approved compound library • Test healthy and diseased population variability in drug effect on cardiac contractility
Statement of Benefit to California (as written by the applicant)	Although heart disease is the leading cause of death in California, decades-old drugs are still mainstays of therapy, despite causing arrhythmia and hypotension. The speedy development of treatments for heart disease is hindered by poorly predictive cardiac heart tissue models. Our tool enables high throughput testing of compounds on heart function for faster and more effective identification of new drugs to treat heart disease, an enormous benefit for the health care of Californians.
Funds Requested	$1,119,382
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All Grants Working Group (GWG) members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 90

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

Mean	89
Median	90
Standard Deviation	2
Highest	92
Lowest	86
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: 11	• This is a robust high-throughput system for drug discovery for cardiomyocytes using iPSC technology. Impressive data. High probability for success. • The proposed tool is designed to create a high throughput cardiac drug screen. In particular, the tool can screen for compounds which may alter cardiac contraction or relaxation rates. This novel tool uses iPS cells grown into cardiomyocytes to create a 3D array in a polymer template in 384 well plates which can contract and act like a cardiac organoid. The 384 well plate play nice with current automation systems. This tool could help to speed the screening of new drugs which could lead to new treatments and reduce the cost of drug development. • Heart disease in the Black and Hispanic ethnic groups continue to be very high in the US. Developing an innovative high throughput heart tissue screening platform would increase the chances of finding new drugs against heart disease. • Very useful screening tool of potentially broad value for cardiovascular drug discovery. • Adoption by other companies of this tool will be important if it becomes available. • It would not directly improve patient care, but could be developed for personalized medicine screens. It has the potential to speed up drug development. It is a unique high throughput screen which can screen for inotropic and lusitropic drugs. The system uses few cells to create the array, further reducing costs. • As a tool it is a ways off to improving patient care, but it has the potential to reduce drug development costs which would be very valuable. • The proposal is a highly innovative approach to fabricate micro heart tissue constructs to behave like human heart tissue which can be used for testing the responses of drugs for improving cardiac function. However, there is skepticism that diseased lines may not have detectable biophysical changes in the proposed system.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 11	• Rationale is sound and was able to answer the previous reviewers concerns satisfactorily. • The preliminary data demonstrates the ability to create 3D cardiac organoids from iPS cells and mature enough to contract. They demonstrate an appropriate cardiac sarcomere morphology and have optimized the size, shape, thickness in a simple well-based strategy to create what they call a micro-heart muscle. They show the physiology of micro-heart muscles within adjacent stencils are independent, beat separately so each micro heart muscle in a well appears to be replicate within a well. They demonstrate an inotropic response of the platform. They plan to explore changes in contractility parameters assayed by pillar movement or optical analysis, such as contraction force/stress, calcium transient amplitudes, and contraction/relaxation rates, this is an important aspect of these studies. • The team has built a lot of background publications and intellectual properties around fabricating micro-heart tissues and the proposal is highly novel. I have not seen anything that is remotely as innovative as this one for making heart tissues from a few thousand cells. The preliminary data is promising with 1 or 2 cell lines with well characterized cardiac functional outputs, and I believe that funding will enable more data to be generated for other cell lines. Yes, the data looks definitely better than 2D cultures and uses fewer cells than traditional embryoid body 3D cultures. • Excellent tool - 3D structures to test multiple disease cell lines.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 11	• The application is improved with a stronger commercialization plan.

	This is an interesting concept and has value as proposed, but information gained from implementation and use of this tool will also drive additional innovation in high throughput cardiac screening tools. • Yes, the proposal is extremely comprehensive and is also a resubmission. They had added two more cell lines to address the diversity of cell line panel so it meets the previous reviewers requests for this diversity. • A two year time line will allow the tool to be fabricated and a library of small molecules to be tested to demonstrate utility. • Good cell assembly, and the option to test contractility and calcium flux with this tool. • Good plans for data management and sharing. • Well designed plan.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 11	• The data shows the feasibility of the approach. • All of the necessary elements are available to complete milestone one on time. Milestone two could be done separate and in parallel to Milestone 1, which will speed up the project. • Although a small team they appear to have the qualifications needed to carry out the aims of the proposal. • They have appropriate letters of support for the manufacture of the plates, access to iPSC and other equipment and support to complete the proposed experiments. • The applicants are well equipped. Their fabrication partner has strong experience in microfabrication of polymeric devices. • They already have shown success with a contract based on a manual system and in negotiation with a very large biotech for a much larger project. The applicant has mitigated the technology risks already. • There is sufficient preliminary data to shown that the tissue is capable of being formed in the novel microstructures for beating heart tissues. However, it is important to make some diseased lines to see how they function. • There will be additional difficulties to culture iPSC with cardiovascular disease in this system. Systems will need to be in place to assess what a quality micro-heart muscle with disease looks like and how to deal with wells that do not meet quality standards. • I believe some of the contractility measures will be difficult in the 384 well plates. Using contraction velocity as surrogate to contractility is not appropriate. They need to look at changes in force as well. It would be nice to see changes in force at various sarcomere lengths, but this would be a very high bar to achieve in a high throughput screen. • Automation/computing power/analysis of changes in micro-heart muscle seem to be very complex to obtain all this information from a 384 well plate. It could take a lot of effort to create this automated high throughput screening laboratory.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 11	• Yes, the team has especially obtained another two ethnically diverse lines as a result of the first review. The challenge is that the cell line supplier needs to get more diverse donors to make stem cells. I am quite sure this will be addressed in the future. Since this has been highlighted in both this and the previous review, we should make it a point that the team focuses their cell line testing with black and hispanic stem cell lines to make cardiac cells in order to make maximum impact of their work. • They have created diverse panels of iPSCs to ensure that undeserved communities are served. • They have added two disease models and two other cell lines from other ethnic origins in addition to male and female cell lines. They have not tested the new cell lines if they will grow, attach and act in similar ways to the current cell lines. • While the cell line used could be expanded to include additional ethnic communities or disease lines, these cell lines are not currently available. Once the tool has be optimized, additional lines could be used. • Neutral now. Potential over time to add in genetic mutations/polymorphisms that may track preferentially with certain underserved communities, and/or add environmental factors (e.g., nicotine) that could be more prevalent in underserved communities.
No: 0	*none*

Application #	TRAN1-12911
Title	Mucopolysaccharidosis type II: Plasma cell delivery of iduronate sulfatase
Translational Candidate (as written by the applicant)	The patient's own B cells will be engineered to express the therapeutic enzyme needed for care in Mucopolysaccharidosis type II (MPS II) patients
Area of Impact (as written by the applicant)	MPS II is a rare genetic disease causing multi-organ symptoms and death by age 15 if not treated. Current treatment does not address the major symptoms.
Mechanism of Action (as written by the applicant)	The proposed therapeutic is a unique combination of cell therapy and genetic engineering. The patient's own B cells are engineered to express the therapeutic enzyme iduronate 2-sulfatase (IDS), which prevents accumulation of glycosaminoglycans (GAG) in various tissues. The cells are then placed back into the patient where they secrete IDS at a therapeutic level. The treatment provides patients with sustained long-term (years) delivery of the therapeutic at levels not seen with other treatments.
Unmet Medical Need (as written by the applicant)	Current treatment for MPS II does not provide therapeutic at sufficient and stable levels, resulting in considerable residual burden of disease. Our treatment will deliver the therapeutic at high, stable levels, and address disease manifestations that are currently not met.
Project Objective (as written by the applicant)	Pre-Investigational New Drug (IND) meeting with the Food and Drug Administration (FDA), transfer to clinical trials
Major Proposed Activities (as written by the applicant)	• Dose-ranging rodent studies to determine the minimal effective and maximal tolerated doses. Effectiveness will be evaluated using established biomarkers. • Long-term efficacy rodent studies (6 months) to characterize treatment effects, including bone manifestations. • Drug product manufacturing, process development and engineering runs to meet specifications. Good Manufacturing Process (GMP) manufacturing of critical reagents.
Statement of Benefit to California (as written by the applicant)	MPS II is a rare genetic disease, with no race or ethnic predilections. Current treatment is expensive ($250K-500K/year/patient) and does not affect key manifestations of the disease. Our approach promises an economical and effective therapy. Our organization has a strong relationship with an MPS II key opinion leader within the University of California (UC) system. We are strongly considering using clinical site(s) within the UC system, because they offer broad reach to diverse communities throughout California.
Funds Requested	$3,994,676
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All Grants Working Group (GWG) members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 88

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

Mean	88
Median	88
Standard Deviation	6
Highest	95
Lowest	75
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	11
(1-84): Not recommended for funding	2

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 11	• Yes. MPS II is an important disease and an unmet medical need. Current therapies are inadequate. The technology could accelerate the development of a stem cell therapy for MPS II. If successful, the product would be a practical value proposition for patients and health care providers. • Lysosomal storage disorders represent a very significant unmet medical need. These are devastating disorders and the rare treatments that are available are both expensive and relatively ineffective. • Yes. Currently available enzyme replacement therapies do not provide sustained levels of iduronate 2-sulfatase (IDS) enzyme and unfortunately do not improve musculoskeletal and nervous system manifestations, or growth. Production of IDS via B cells may provide continuous and sustained delivery of therapeutic IDS, which could address these unmet needs. • Success in this project would not only increase the likelihood of moving forward with a treatment for MPS II, but would also represent the development of a strategy that could be rapidly applied to other lysosomal storage disorders. • Yes, for MPS II and for other lysosomal storage diseases. • I really appreciate the novelty of this application.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 11	• Yes, it is well established that MPS II causes the pathologic accumulation of glycosaminoglycans (GAG) in organs and tissues leading to multiple disease pathologies. Enzyme replacement therapy has demonstrated positive benefits from clearance of GAG. • The applicants' plan for genetic modification of B cells represents an elegant way of harnessing the ability of B cells to produce large amounts of specific proteins. With this approach there is a possibility of achieving high levels of enzyme production and secretion. • The long-lived nature of B cells is another positive feature of this approach. • The applicants put forward a good rationale for widespread tissue distribution by plasma cells. • The data are strong. They are able to modify B cells successfully and transplanted cells are able to secrete high levels of IDS. In addition, transplantation of the candidate for this proposal into MPS II model mice shows significant reductions in tissue GAG levels and high tissue levels of IDS. • There is still a question as to whether any of the enzyme will get into the brain. This has not yet been shown. • They have not yet established batch-to-batch variability of the proposed product, or requirements for acceptable production of the cells needed. More research is required in this regard. • The animal model is not yet fully described and requires further assessment. • Engineering of B cells is a rational approach for the production of the IDS protein. However, I am concerned about the feasibility of their specific genetic engineering approach, which is known to be immunogenic. The promising rodent model data are early and do not establish potential efficacy because the rodent model is not one that would reveal immunogenic issues with this genetic approach. • Immunogenicity of IDS cannot be assessed in the rodent model.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 10	• Yes. The program has very strong scientific and translational foundations from a related program involving treatment of MPS I.

	• The project is well planned and designed, and benefits from the previous work from this team on developing a similar treatment approach for MPS I. • Yes, the project milestones are well-defined and should result in meaningful FDA pre-IND meeting. • One slight issue is that the model rodents will not uncover any immunogenic issues from the transplantation. The genetic engineering approach they have chosen is possibly immunogenic. • Would it improve safety to introduce a "suicide" gene in case of unexpected malignant transformation of any of the engineered B cells?
No: 1	• The possibility of B cell transformation to malignant cells should be more seriously considered in the project plan.
GWG Votes	**Is the proposal feasible?**
Yes: 11	• The applicant presents data showing achievement of wild-type IDS tissue levels after treatment in immunodeficient MPS II model rodents with corresponding reduction in tissue GAG storage. Additional data is presented from a related program in MPS I that suggests similar data should be achievable in MPS II. • Studies on another therapeutic candidate, for the treatment of MPS I, demonstrated sustained tissue activity for six months after treatment and a sustained reduction in levels of glycosaminoglycans in this mouse model. • Based upon the previous activities in developing a similar kind of a treatment for MPSI , there is a reasonable expectation of success in the proposed effort.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 11	• Lysosomal storage disorders do not distinguish between different human populations and these therapies are needed across the board. • Because the cells used will be from each individual patient, this will be available to all communities. • The applicants have plans to ensure that harder-to-reach populations might be recruited to studies. • The company has identified plans to engage with the National MPS Society and key opinion leaders to promote recruitment among underserved populations. They will also provide travel and accommodations to families of participants. • The investigators address this issue satisfactorily.
No: 0	*none*

Application #	TRAN1-12895
Title	Hematopoietic Stem Cell Gene Therapy for Immunodysregulation Polyendocrinopathy Enteropathy X-linked (IPEX) Syndrome
Translational Candidate (as written by the applicant)	Human hematopoietic stem cells that have been modified to express a functional replacement gene to treat patients with IPEX syndrome.
Area of Impact (as written by the applicant)	These studies will bring stem cell gene therapy for IPEX syndrome closer to the clinic, especially for patients without a bone marrow donor match or disease too severe for hematopoietic stem cell transplantation (HSCT).
Mechanism of Action (as written by the applicant)	Hematopoietic stem cells (HSC) with defective expression of the gene FoxP3 are modified with a viral vector which restores a normal copy of the defective gene. Transplantation of these gene-modified HSC, which are self-renewing and long-lived, produce all blood lineages, including regulatory immune T-cells with restored FoxP3 expression. These T-cells can abrogate the severe autoimmunity present in IPEX Syndrome.
Unmet Medical Need (as written by the applicant)	There is no curative treatment for IPEX syndrome patients without a bone marrow match. Gene-corrected HSC can cure IPEX and provides a therapeutic option for these patients. This proposal will advance the field of stem cell gene therapy and treatment of primary immune disorders.
Project Objective (as written by the applicant)	Pre-Investigational New Drug (IND) meeting with the Food and Drug Administration (FDA)
Major Proposed Activities (as written by the applicant)	• Obtain clinical grade viral vector and demonstrate the ability to manufacture the stem cell product at clinical scale • Perform rodent studies to assess safety and the effective dosage of the cell product • Prepare clinical protocol, investigator's brochure, consent forms, and Pre-IND package. Complete Pre-IND meeting with the FDA
Statement of Benefit to California (as written by the applicant)	Safe, definitive therapies for IPEX syndrome represent an unmet medical need. Allogeneic stem cell transplantation is frequently complicated by graft-versus-host disease or limited by lack of matched donors. Successful demonstration that stem cell gene therapy can safely and effectively cure IPEX will shift the paradigm by which patients will be treated and provide a foundation by which other immune and blood diseases may be cured in the future.
Funds Requested	$3,551,332
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All Grants Working Group (GWG) members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 86

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

Mean	86
Median	86
Standard Deviation	2
Highest	89
Lowest	83
Count	12
(85-100): Exceptional merit and warrants funding, if funds are available	10
(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: 10	• Yes, this is an unmet clinical need. The current therapy for IPEX syndrome is hematopoietic stem cell transplantation (HSCT) with immunosuppressive therapy. The disease is often fatal within the first two years of life with pathology leading to multi-organ autoimmunity manifesting via hemorrhage, or sepsis. Chronic immunosuppression often provides only temporary benefit. Allogeneic HSCT can be curative but is limited by the availability of suitable donors. The investigator proposes a curative therapy for patients with IPEX syndrome. • IPEX is an extremely rare condition in males that is caused by the inactivation of the FoxP3 gene on an X chromosome (thus it is male specific). Patients are given allogeneic HSCT with concomitant immunosuppression, but nonetheless IPEX is normally fatal within the first 2 years of life. • IPEX syndrome is a rare disease with only 200-300 cases worldwide. • This project will obviate the need for immunosuppression in IPEX patients, and will also allow patients to be treated when there is no appropriate donor match. Therefore, I believe the project is significant and has the potential for significant impact in the IPEX patient population. • This project is significant because the applicants intend to insert a functional FoxP3 gene into patients' own HSCs using virus technology. • It's not clear on how impactful this treatment will be with so few patients. Knowing if there is practical value is a struggle, and there is no validated financial model for comparing HSCT with gene therapy. • There are several IPEX related projects (costing 5-10 million dollars) competing against this project. This competition may diminish the value proposition. • It is important to support programs for ultra-rare diseases as well as more common ones. It would be helpful for the applicants to give greater clarity on what may be learned that will also potentially impact more common diseases. For example, here they plan to create a Treg product, which has not been achieved in many other contexts to date. • This is an ultra-orphan indication, and therefore of limited applicability. • The project meets an unmet need for a rare disorder, plus the field could learn lessons for treating more common conditions. • Although IPEX is a rare disease, this therapy will be highly impactful in those patients with the disease. It may have impact in the wider T-cell and regulatory T-cell biology world.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 11	• Yes. The applicants have provided strong supporting information for their approach. • This study has a good scientific rationale. The pilot data are compelling. • The rationale is based on the applicants' prior project, plus pilot/new data that suggest that FoxP3 can be integrated into HSC which then differentiate into suppressive regulatory T-cells. This finding is bolstered by their other data and references. Their vector seems to be lineage specific. • The rationale is based on significant pre-clinical data in animal models. The hypothesis is simple enough- replace a dysfunctional gene with a functional gene in an appropriate cell population which should lead to the production of T-cells currently missing in IPEX patients. • The investigators are assessing viral vector-transduced autologous HSPC to restore FoxP3 expression. The applicants have addressed points and added suggested studies from an FDA INTERACT meeting, which could accelerate the time to a definitive study execution.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**

Yes: 11	• One of the major strengths of the project is that they have already had an INTERACT meeting with the FDA. They have taken notice of everything the FDA suggested for planning their studies, and are progressing towards a pre-IND meeting. • The applicants have aligned with suggestions from INTERACT. They will now conduct their planned studies with the clinical product, and will utilize the appropriate disease model for preclinical studies. • Yes. It was thoughtful and helpful to have had the INTERACT meeting. • The applicants have had an INTERACT meeting and have been responsive to the advice from FDA. Their use of experienced contract research organizations (CRO) adds to my confidence that they will likely complete the project. • There is not a lot of manufacturing process information in the application, but they are using very well-credentialed CRO and contract manufacturing organizations (CMO) so I feel satisfied that manufacturing issues will be adequately covered. • The investigator suggests efficacy and safety assessments with appropriately graded critical reagents. They plan to assess toxicology with a cell product produced at clinical scale. Dosing studies will need to be executed with the appropriate final product. • The applicants were able to meet their current benchmark for clinical efficacy in the intended human cells through development of FoxP3 knockout progenitor cells from healthy donors. They will move forward with this model to fulfill FDA pre-IND suggestions including starting dose. • Overall the project is appropriately planned with a goal of developing Good Manufacturing Practice (GMP) products. • Milestone are clear and appropriate.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 11	• The applicants' proposed 2 years to move to pre-IND appears to be reasonable, and they have included a possible 6 to 9 month extension in their contingency planning). This is a highly qualified team. • The assembled team is excellent. • This team has viral vector and regulatory experience, plus they will be using CRO to facilitate. • Yes, the pilot data are compelling and support making a clinical product. • Yes. While ultimately the clinical trial may prove difficult in terms of patient recruitment and costs, the proposal is feasible. • I do believe the project is feasible. Looking forward into the clinic, given this condition is so rare I do wonder if the applicants will have issues with recruiting adequate numbers of subjects.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 9	• The applicants made an excellent effort to interrogate databases to identify if this is under-diagnosed or underreported in underserved communities. • The applicants have pointed to some evidence that IPEX syndrome is not well-diagnosed in underserved communities. The applicants intend to address this problem when this project is ready for the clinic.
No: 2	• IPEX syndrome is a very rare disease, so the inclusion of underserved communities is hard to address with certainty. • Generally, no. This is only because IPEX syndrome is so rare and thus this project's impact will be limited.

Application #	TRAN1-12890
Title	Clinical translation of human embryonic stem cell-derived protein therapy that positively regulates the regenerative capacity of post-natal muscle for treating myotonic dystrophy type 1 (DM1)
Translational Candidate (as written by the applicant)	An engineered stem cell-secreted signaling protein for treatment of skeletal muscle disorders
Area of Impact (as written by the applicant)	Skeletal muscle disorders (including DM1 and sarcopenia) remain major unmet needs that require treatments restoring muscle strength and function.
Mechanism of Action (as written by the applicant)	Our animal data demonstrate that endocrine stimulation by our endogenous muscle precursor cells restores muscle stem/precursor survival and differentiation, counters muscle atrophy, and improves muscle strength/endurance in multiple disease models. This process is impaired in age-related and degenerative skeletal muscle diseases including DM1 and sarcopenia.
Unmet Medical Need (as written by the applicant)	DM1 is the most common muscular dystrophy in adults, affecting an estimated 1 in 2,532 people in the United States, slowly depriving patients of their ability to walk, use their hands, and breathe - and yet this population is without treatment options.
Project Objective (as written by the applicant)	Pre-Investigational New Drug (IND) meeting
Major Proposed Activities (as written by the applicant)	• Develop Good Manufacturing Process (GMP) compatible process and non-GMP production • Qualification of assays for manufacturing process, release potency, and pre-clinical studies • Perform pre-clinical toxicology, biodistribution, safety, potency, and efficacy studies
Statement of Benefit to California (as written by the applicant)	DM1 is the most common muscular dystrophy in adults, affecting an estimated 1 in 2,532 people in California, slowly depriving them of their ability to walk, use their hands, and breathe. California has the largest population of persons with DM1 of any state, and is home to the Myotonic Dystrophy Foundation representing and building support for the needs of the thousands of Californians severely medically and financially impacted by this debilitating disease.
Funds Requested	$3,906,376
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All Grants Working Group (GWG) members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 85

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

Mean	85
Median	85
Standard Deviation	1
Highest	87
Lowest	85
Count	12
(85-100): Exceptional merit and warrants funding, if funds are available	12
(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: 11	• The proposed product is being developed to treat a variety of conditions that primarily affect skeletal muscle, including age-related degeneration and muscular dystrophies, in particular myotonic dystrophy type 1 (DM1). • In aggregate these conditions affect roughly 2 million Californians per year. • These conditions greatly impact quality of life, can shorten lifespan significantly, and impose very substantial burdens to the healthcare system in cost and demand for infrastructure. • A possible first indication for the project is DM1, is a genetic muscle degenerative disorder with a functional profile similar to age-related muscle degeneration. • DM1 affects about 1:2,500 individuals. The most severe forms of the condition are life-threatening, and milder forms impose major burdens. • At present there are no well-established effective treatments for either age-related muscle degeneration or DM1. • The product is intended to activate endogenous muscle stem cells - thereby restoring or preserving in patients an otherwise declining capacity for independent walking, swallowing, and/or breathing. • This product is being developed as an off-the-shelf protein therapeutic. If successful, the product will be used by a broad swath of the DM1 patient population and benefit patients and health care providers.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 10	• This proposed biologic therapeutic is based on sound scientific principles. • The biologic candidate is a protein agonist that activates the major signaling pathway in regenerating skeletal muscle. Receptors for the candidate biologic are expressed by muscle precursors in aged humans and those with DM1. • The assessment conducted by a consultant is a nice way to prioritize target indications and nicely shows the rationale for going after DM1 in the initial trial. • Some of the background literature contradicts the rationale for the therapeutic use of the target pathway. For example, there are reports that activating this cell signaling pathway may ameliorate Duchenne muscular dystrophy (which is entirely distinct from DM1) in mice; yet, a recent paper reports that blockading this cell signaling pathway actually improves muscle regeneration and ameliorates the Duchenne muscular dystrophy phenotype in a model mouse. This latter result would apparently run counter to this project's rationale, in at least some degenerative muscle conditions. Implications for DM1 or sarcopenia are not clear. • The engineering of a protein biologic with significantly improved pharmacokinetic properties strengthens the rationale. However, the *in vitro* data are not very convincing of a dose response. • The preclinical study in the cardiotoxin model used intramuscular injection of the short-lived analog of the candidate therapeutic, and it is not clear how relevant this data is to the administration of the final drug by subcutaneous route. • Although preliminary, the existing *in vivo* data do show statistically significant differences in treated mice as compared to controls, and the selected parameters appear relevant. However, it is unclear if the effect size observed will translate to a clinical benefit in humans, especially as there is no positive control (i.e. non-aged adult mice) in the study. Also, the treatment effect was highly variable between mice. • Yes. However there are some key controls missing from some of the studies. These will likely need to be fleshed out in the proposed efficacy-testing studies. For example, in Figure 3, the applicant claims that "expression of the receptors for [the candidate] does not decline in aged or dystrophic (DM1) muscle precursor cells." Yet, they only look for expression of these receptors using RNASeq, and not at the protein level.

No: 1	• Some study controls are missing, which raises concerns about the scientific basis for the rationale. • The efficacy models are not that compelling.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 11	• Milestones and the Project Plan are laid out well to address key areas for product development: 1) Pharmacokinetics, including necessary assay development; 2) Chemistry, Manufacturing and Controls and process development to be carried out by a subcontractor, including process development and generation of master cell banks; 3) pilot safety experiments in mice and non-human primates; 4) efficacy studies in a recently published inducible model of DM1; 5) regulatory strategy targeting a Pre-IND meeting with the FDA. • Yes, the project is well planned and, if successful, will result in a meaningful milestone (pre-IND meeting). • The Target Product Profile is overly broad, with multiple examples of indications where the product could promote muscle regeneration or prevent degeneration. However, the applicants include a well thought-out table and heat map that provide the basis for prioritizing DM1 as the first indication. • The heat map showing priority indications includes a red flag for regulatory issues in trials of DM1. This potential complication is not addressed in the proposal. • An INTERACT meeting with the FDA would be beneficial. • I would have liked to see more dose range studies. How can daily injections in mice translate to the weekly human dose? • This is a well-planned body of work but there is uncertainty about the unproven new mouse model.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 11	• This is large team with key inventors and drivers of the program working in a small biotechnology company, which currently resides within the institute's incubator. • The company founders have done leading work in aging and regeneration. • Most of the product development, animal study, and regulatory activities are contracted to well-established Contract Research Organizations (CRO). Coordination of the activities will be challenging, but appears achievable. • The application addresses many contingencies: production of the recombinant protein candidate, project governance, assay development, validity of the biological test for activity against DM1, and the risk that the product will not clearly demonstrate efficacy in the mouse model. • There is a reasonable fallback strategy to shift focus to sarcopenia, but this would likely extend beyond the time and financial scope of the requested grant. • The report of Pre-Series A funding and the receipt of a small business grant gives some concrete assurance of the company's financial stability.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 10	• The team includes individuals who are the first in their families to achieve advanced degrees and/or to participate in entrepreneurial biopharmaceutical ventures. • The applicants discuss strategies for inclusiveness in clinical trials in general terms, i.e,, the project plan mentions that the sponsor hopes to enroll as many patients with adult-onset DM1 as possible “regardless of ethnicity or socioeconomic status.” • The applicants' focus on a product that would benefit the elderly is another positive aspect of inclusiveness.
No: 1	*none*

Application #	TRAN1-12987
Title	Chimeric Antigen Receptors (CAR) for the treatment of refractory pediatric B-cell acute lymphoblastic leukemia
Translational Candidate (as written by the applicant)	Targeting chimeric antigen receptor (CAR) T cells incorporating fully synthetic nanobodies
Area of Impact (as written by the applicant)	Pediatric B-cell acute lymphoblastic leukemia refractory to currently available treatments without other potentially curative options
Mechanism of Action (as written by the applicant)	The proposed candidate functions as Chimeric Antigen Receptor (CAR) T cell. When the CAR-T cell recognizes tumor cell expressing the designed target, they are activated and lyse the tumor cell. These "living drugs" can potentially multiply and persist within the body to eliminate tumor cells for long periods of time, or even lead to cures in patients with previously dire prognoses.
Unmet Medical Need (as written by the applicant)	Children and young adults with B-cell acute lymphoblastic leukemia who relapse on available therapeutics need new options for survival. Our therapy aims to address this unmet need through a newly-discovered target and new type of cellular design.
Project Objective (as written by the applicant)	Pre-Investigational New Drug (IND) meeting with the Food and Drug Administration (FDA)
Major Proposed Activities (as written by the applicant)	• Process development for manufacturing of CAR T-cells. • *In vitro* and *in vivo* studies to determine preclinical efficacy and safety of the therapeutic candidate. • Development of the validated target assay, clinical trial protocol, consent form and clinical Standard Operating Procedures (SOP).
Statement of Benefit to California (as written by the applicant)	The goal of our project is to develop a new therapy for pediatric cancer patients who currently have no other good options. We anticipate this therapy would potentially benefit dozens of children per year in California. Furthermore, successful development of this therapy under the goals of this CIRM award could open its use to an even broader set of children and adults with cancers the express our target of interest, potentially impacting hundreds of individuals per year in our state.
Funds Requested	$3,330,801
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All Grants Working Group (GWG) members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 85

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

Mean	85
Median	85
Standard Deviation	2
Highest	90
Lowest	80
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	11
(1-84): Not recommended for funding	3

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 12	• The team has clearly established that there is an unmet medical need in myelomastocytic leukemia rearranged B-cell acute lymphoblastic leukemia (MLLr B-ALL), particularly pediatric and young adult patients who relapse after current therapy. • The proposal addresses an unmet medical need. About half of pediatric patients who received standard of care anti-CD19 CAR-T cell therapy have relapses 6-12 months after therapy. This category of patients has no other therapeutic options. • The unmet need is B-cell acute lymphoblastic leukemia (B-ALL) that has relapsed after CD19 CAR-T cell therapy. • Treating refractory B-ALL in children would have impact. The standard of care currently is CD19 CAR cells but there is relapse. Will this be able to treat this cohort? They have not made it clear whether patients receiving the product should have had anti-CD19 before. • The addressable patient population (market size) is very small. If the target is right, a new product could replace the first generation marketed CAR-T. • The authors should acknowledge not only their target as an alternative to CD19, but multiple developments of bi- and tri-specific CARs. The current development environment is very dense and competitive.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• The preliminary data are supportive. • Excellent bioinformatic approach to identifying a possible target. • The team has clearly established that the target is highly expressed on B-cells and in few other tissues. • The proposal is supported by preliminary data. However, there is a minor flaw in the design of the series of new proposed experiments. The current standard anti-CD19 CAR should be included as it was used in the pilot efficacy/safety study (#1). The authors are planning to compare only therapeutic analog versus therapeutic candidate. In the *in vivo* B-ALL model standard anti-CD19 CAR outperformed the therapeutic analog, as shown in Figure 8. • It is not clear whether the target can undergo antigen escape, as has been observed with anti-CD19. • The product could be improved further if the binding domain could be fully human. The authors mentioned that the current standard murine binding domain has only 60% of human homology and this could be one of the reasons for relapse. However, the proposed product would increase human homology only to 80%. Why not design a fully human binding domain? • Some aspects related to the patient selection and treatment sequence remain unclear.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 12	• Yes, the team has outlined all the elements that will need to be addressed for a productive pre-IND discussion with FDA including plans for pilot manufacturing of the therapeutic candidate, plans to repeat key preclinical proof of concept studies using the therapeutic candidate, a reasonable outline of preclinical pharmacology and toxicology studies and an outline of a phase 1 clinical study. • The project is well planned and designed. • Why is the proposed trial not going to be enriched for myelomastocytic leukemia rearrangements? • Competing solutions not adequately addressed.

No: 1	• It is not clear whether the target patient population has failed anti-CD19 CAR-T. It seems that it would be difficult to enroll a patient on a novel CAR-T therapy trial when there is a CAR therapy that is already FDA-approved and represents the standard of care. This clarification should be considered in the preclinical modeling (i.e., anti-CD19 CAR-T therapy failures) as well as within the protocol development.
GWG Votes	**Is the proposal feasible?**
Yes: 13	• Yes, the proposed milestones appear to represent a logical progression of activities necessary to support a pre-IND with the FDA. • The project looks feasible. Milestones are reasonable.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 12	• Efforts planned related to using existing mechanism for enrolling underserved populations. • They state that the patient population served at the institution reflects the diversity of California and they will strive to include our diverse patient population in this clinical trial.
No: 1	*none*

Application #	TRAN1-12893
Title (as written by the applicant)	Targeting stromal progenitors to prevent the development of heart failure
Translational Candidate (as written by the applicant)	Monoclonal antibody
Area of Impact (as written by the applicant)	Heart disease: The development of heart failure after heart attacks
Mechanism of Action (as written by the applicant)	After myocardial infarction (MI), myofibroblast progenitors express a transmembrane protein that initiates an inflammatory cascade that inhibits cardiac repair. The candidate monoclonal antibody would bind to this transmembrane protein on myofibroblast progenitors and inhibit signaling, to decrease inflammation and scarring and augment heart repair and post-injury heart function after myocardial infarction (MI).
Unmet Medical Need (as written by the applicant)	Approximately 6 million people in the United States have heart failure (HF). Once a diagnosis of HF is made, approximately 50% of patients survive 5 years or longer. There an unmet need for novel therapeutics for HF. The monoclonal antibody candidate we are developing is intended to prevent the development of HF after heart attack.
Project Objective (as written by the applicant)	Pre-Investigational New Drug (IND) meeting
Major Proposed Activities (as written by the applicant)	• Development of a stable cell bank for antibody production • Upstream and downstream process development • Dose range finding studies
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. Seven percent of individuals above the age of 65 suffer from heart failure. Heart attacks (myocardial infarctions, or MI) are the leading cause of heart failure. Our candidate antibody therapy has the potential to prevent the development of heart failure after heart attacks and be of immense benefit to Californians.
Funds Requested	$4,841,428
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All Grants Working Group (GWG) members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 85

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

Mean	84
Median	85
Standard Deviation	5
Highest	90
Lowest	75
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	9
(1-84): Not recommended for funding	6

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 10	• Myocardial infarction (MI) creates areas in the heart which can no longer contract and may be subject to thinning and rupture. Most importantly, after MI a scar can form, which is resistant to further remodeling/repair by stem cell-based or other treatments. A product that could alter this process would impact an unmet medical need. • This project may serve as an adjunct to stem cell therapy by reducing the MI scar size and/or allowing stem cell engraftment. • Anything that would reduce scar size could be helpful, assuming it is accompanied by improved cardiac function and/or improved efficacy of other therapies. • While not a stem cell therapy in itself, the approach has the potential to impact cardiac remodeling. • Inhibition of remodeling post-MI would be high-impact. • The project addresses an unmet medical need with a novel therapeutic approach.
No: 4	• It is not clear that this approach would be superior to existing inexpensive therapies. • The translation of this approach to heart failure is really far away. • This is not a regenerative approach.
GWG Votes	**Is the rationale sound?**
Yes: 13	• Based on the resubmitted proposal, the project has a reasonable scientific rationale and a pathway forward that will result in a successful pre-IND meeting. • An inhibitory antibody is being developed to decrease myofibroblast inflammatory activity which may decrease heart injury and scar size and may increase healing after MI. Available data demonstrate this to be possible and suggest a mechanism of action. • The mouse model data appear to support reduction of scarring/remodeling. • Reviews for the original submission included concerns about the safety of inhibiting the repair process post-MI due to risk of myocardial rupture. The applicant's revised plan to conduct studies in a large animal model will help to alleviate those concerns. • The original reviews also suggested inhibition of myocardial fibrosis with this therapy might be better suited to other forms of heart failure, e.g. hypertensive cardiomyopathy, sarcoidosis, rather than post-MI. The applicants have added a hypertensive mouse model to the proposal. However since the target transmembrane protein expression peaks 7 days post-MI, this antibody approach might not be effective in slower-developing models of fibrosis. • They have added data using a pressure overload model of hypertrophy showing improved cardiac function in treated mice. However, antibody treatment was started 7 days post overload, which is when the target protein expression peaks (from 7 to 14 days). This study may not be a good test for longer standing cardiac hypertrophy models. However, showing efficacy in a second model overall strengthens the proposal. • According to the revised proposal, administration of the antibody at various intervals (days to weeks) post-MI will be tested to assuage previous reviewers' concerns about scar rupture and to characterize the time period when this therapy could be applied.
No: 1	• There is some merit to the applicant's approach, but why not compare against current standards of care? These are inexpensive and fairly effective.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 11	• This is a good resubmitted design; the applicants have been responsive to the prior feedback. • Based on the revised package, the project has a pathway forward that will result in a successful pre-IND meeting. Likewise, the approach will allow for reasonable go/no go milestones. • The applicants propose pharmacokinetic, pharmacodynamic and toxicology studies of the fully humanized monoclonal antibody in humanized mice as well as streamlined safety studies in mice and larger animal models. All important and necessary studies.

	• They plan to determine the optimal duration of therapy with the humanized antibody following myocardial infarction, treating for up to 6 weeks. Another necessary step. • They will determine how long therapy can be delayed after myocardial infarction to get the same benefit. This is a very important step which will determine if knockdown of high (acute) protein expression levels are critical to the therapy. • They will also determine efficacy of the mAb in non-ischemic cardiomyopathy and in a larger animal model of myocardial infarction. Both studies have been requested by previous reviewers and will help determine if the product should move to clinical trials. • The manufacturing process development and scale-up appear sufficient to supply a phase 1 study. Associated analytical development is proposed and needed. • They have added a safety expert, who is also guiding them in the pre-IND package. The expert's guidance has helped to focus and refine the experiments proposed. • This is a compact timeline. With many experiments to run, the project will be difficult to complete in 30 months.
No: 3	• There is no comparison with existing therapies. Would this antibody be additive to standard of care?
GWG Votes	**Is the proposal feasible?**
Yes: 13	• All the pieces are now in place to move this project forward. • Letters of support and other resources and funding contingencies are in place to conduct the studies. However, since work is being done at contract research organizations (CRO), delays beyond the applicants' control could cause issues. Switching CRO (as they suggest) to alleviate such issues would add significant delays and might not be straightforward. • With some studies performed at CRO, the timelines, while tight, can be achieved. • Ambitious timelines; good team.
No: 1	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 14	• For a project at this stage, they adequately address race, ethnicity and gender concerns. • Cardiac disease has an increased prevalence in underserved communities and any effective product would be a benefit. The product should be cost-effective, further helping all populations. • MI disproportionately impacts underserved communities. • This project will positively impact underserved communities.
No: 0	*none*

Application #	TRAN1-12920
Title (as written by the applicant)	Development of a gene editing therapy for Duchenne muscular dystrophy
Translational Candidate (as written by the applicant)	A gene editing therapy for Duchenne muscular dystrophy (DMD) that permanently removes a hotspot region of patient mutations to restore dystrophin.
Area of Impact (as written by the applicant)	Duchenne muscular dystrophy (DMD), a fatal muscle wasting disease with no cure.
Mechanism of Action (as written by the applicant)	Our therapy uses gene editing to permanently remove a hotspot region of DMD patient mutations, which reframes the gene and restores expression of the dystrophin protein. This approach targets the underlying cause of disease by removing out-of-frame mutations that otherwise would result in a lack of dystrophin protein and Duchenne disease progression. Thus, restoration of dystrophin using our approach is expected to repair and regenerate damaged muscle in DMD.
Unmet Medical Need (as written by the applicant)	Our therapy is for Duchenne muscular dystrophy, a fatal muscle wasting disease with no cure. There are only a few approved therapies, a corticosteroid (standard of care; slightly improves progression) and exon skipping drugs (only for 8-13% of patients; modestly effective with ~1-3% dystrophin).
Project Objective (as written by the applicant)	Pre-Investigational New Drug (IND) meeting
Major Proposed Activities (as written by the applicant)	• Assessment of efficacy, pharmacology and safety in rodent and canine models • Assessment of off-target editing in human cells • Development of a potency assay and manufacturing partnership
Statement of Benefit to California (as written by the applicant)	This proposal will advance preclinical development of our gene editing therapy for Duchenne muscular dystrophy (DMD). DMD is a devastating muscle wasting disease leading to premature death in the 20-30s. It affects approximately one in 5000 boys worldwide, thus there is a fairly high concentration of DMD patients in California. There is currently no cure and only a few approved therapies with limited benefit, thus there is a need for disease modifying therapies that aim to restore dystrophin.
Funds Requested	$3,400,000
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All Grants Working Group (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	3
Highest	90
Lowest	78
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	9
(1-84): Not recommended for funding	4

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 11	• If the proposed product is successful, it would be a much needed treatment for a significant number of Duchenne muscular dystrophy (DMD) patients. • Yes, this is a disease with no cure that needs new therapy options. • The genome editing strategy is novel and complex. • Meets a large unmet need. • There are concerns with toxicity issues. If they need a high dose to have effects, this will likely be problematic. The large animal biodistribution study in the project plan will show how toxic the therapy really is. The canine model studies will also be critical. It would be important to do these studies since this is truly a disease with no options, so worthy of further development despite the caveats above.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 10	• The rationale is ingenious and novel and overcomes many limitations of previous strategies. • The overall science behind their approach is sound and in keeping with a few already approved products. • The data presented strongly support the feasibility of the approach. Proof of concept has been demonstrated, sufficient to warrant further investigation into this approach. • There is evidence that some level of dystrophin production can be restored by the gene correction strategy. This is a complex gene correction though and likely to be comparatively inefficient with large amounts of cells that do not receive all the edits which would be needed for functional outcome. • The deletion strategy is sound. • I wished they shared the animal biodistribution and toxicity report for Figure 6 in rodents. It is highly possible that they will see toxicity, but rodent efficacy study #4 had restoration of dystrophin and no overt toxicity.
No: 1	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 9	• The investigators have created a well-designed plan that goes a long way to satisfy the requirements of a pre-IND meeting. • Overall, this approach has potential. The cellular and molecular aspects, which make up the vast majority of the proposal, seem very well considered and thoughtfully designed. • The program is well designed and although there are limitations to the animal models for testing, nevertheless the data should provide strong evidence for whether clinical trials are warranted. • The canine model is usually used as a functional model - but not used this way in this proposal - why not? Is it justifiable to use if not for function? • The absence of any functional assessment is a major weakness, one that will have to be addressed if the goal is a successful IND. Indeed, there is almost no justification for the use of a canine model. • Trying to obtain functional data will be important in upcoming preclinical studies. • Overall yes, but the applicants need careful safety considerations for systemic administration. Is there evidence that the vectors will work in children (the target population) in their growing tissues with dividing cells? • Could use more focus on safety and, ideally, comparison with other therapies such as exon-skipping. • Cardiorespiratory failure is also the leading cause of death for DMD patients, and while the absence of a cardiac phenotype in the selected models makes assessing this difficult, it should have received some level of consideration. • Any correction effect on cardiac and respiratory skeletal muscles is not addressed.

No: 2	• More detailed quantification on the spectrum of genetic outcomes is needed.
GWG Votes	**Is the proposal feasible?**
Yes: 10	• Yes, this is a feasible project as currently proposed and could successfully reach the stated milestones to achieve a working product. • Excellent team. • Highly qualified team. • The timelines are a little optimistic, but doable. • The contingency plans are adequate. There will likely be anticipated delays due to the complexity of the animal models and the interpretation of the data to support the IND.
No: 1	• The viral loads to reach high efficiency with the dual delivery system are likely to have serious safety concerns.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 11	• Yes, this project is consistent with CIRM goals. • Strong plan. • The company itself is headed by a diverse team, and the applicants plan to collaborate with organizations already active in underserved communities for future recruitment. However, DMD is a disease where the vast majority of patients are boys or young men, and with white or caucasian families being more significantly affected.
No: 0	*none*

Application #	TRAN1-13059
Title (as written by the applicant)	A human neural stem cell therapeutic candidate for the treatment of chronic cervical spinal cord injury
Translational Candidate (as written by the applicant)	The therapeutic candidate is a central nervous system tissue-derived Good Manufacturing Practices (GMP) line developed under a prior CIRM grant with an established GMP qualified seed bank.
Area of Impact (as written by the applicant)	The target is chronic cervical spinal cord injury, which represents approximately 59% of clinical spinal cord injury cases.
Mechanism of Action (as written by the applicant)	Integration of transplanted human neural stem cells is likely to direct improved locomotor function by a combination of mechanisms that include the production of new myelinating cells. Transplanted neural stem cell survival, migration, and formation of new oligodendrocytes have been linked to repair capacity.
Unmet Medical Need (as written by the applicant)	There are no Food and Drug Administration-approved treatments for spinal cord injury. There are roughly 285,000 individuals living with paralysis due to traumatic spinal cord injury in the United States, with as many as 20,425 in California at a projected collective lifetime cost of $104 billion in direct and indirect costs of care.
Project Objective (as written by the applicant)	Submission of a Pre-Investigational New Drug (IND) package and completion of a Pre-IND meeting.
Major Proposed Activities (as written by the applicant)	• Establish critical process parameters for therapeutic candidate expansion and establish GMP final product bank. • Complete pre-clinical testing of final product cells and conduct preliminary testing of assays for potency and comparability during cell production. • Test a clinical strategy to improve engraftment and reduce rejection after allogeneic cell transplantation into the central nervous system.
Statement of Benefit to California (as written by the applicant)	We seek to develop a new human neural stem cell therapeutic for chronic cervical spinal cord injury, for which there are no approved treatments. Improvement of a single level of spine function could have a large effect, significantly impacting both quality of life and the economic burden of disease. We also seek to develop new clinical strategies for monitoring potency during cell production and allogeneic cell transplantation, broadly impacting cell based therapies for neurological conditions.
Funds Requested	$5,552,611
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All Grants Working Group (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	90
Lowest	75
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	8
(1-84): Not recommended for funding	5

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 10	• There is a great need for treatments for chronic spinal cord injury (SCI). This medical condition causes great personal and financial cost, and there are no current treatments. • If the treatment period can be extended out to 30 days post-injury, this would be a major advance. Current treatments that have moved into clinical trials need to be initiated long before this. • An important area of research but more scientific understanding is needed before proceeding towards the clinic. The worst outcome would be prematurely entering a clinical study that generates more negative results and sets the field back further. • Currently there are few sponsors pursuing neural stem cells (NSC) in SCI due to prior underwhelming studies. The logic of the application is that if we do a better job picking cell lines, there will be more clinical recovery. It would seem that the effect size would need to be very compelling in a unilateral lesion model in mice to have a chance at human efficacy. SCI is not an injury that has a direct curative target. Lesion region cell transplantation is a very over-simplified approach. • It is possible to find reasons for concern about this application. Is there neuroprotection? Cell replacement? Making sick cells healthier? We don't know - but maybe those are not the right questions. In this vein, the real question is behavioral recovery, regardless of the mechanism. Here, the data look very promising. • Important disease.
No: 1	• The clinical studies to date with cell therapies in this class do not indicate that this strategy would have a high impact.
GWG Votes	**Is the rationale sound?**
Yes: 8	• The rationale rests on the premise that some fetal NSC will be much more effective than others. • The idea of using NSCs for this effort is sound, because they can make multiple cell types. Whether their ability to generate oligodendrocyte-lineage cells is critical in their benefits is unclear, but the fact is that we know little about how benefits are provided by most pro-reparative cells. • It is possible the injection of NSCs as a strategy will have limited efficacy. The absence of evidence of tissue formation in a condition that requires tissue reconstruction is a serious concern.
No: 3	• I did not see evidence in the resubmission that strongly supports moving the current product concept towards the clinic at this time. • There is no evidence of new tissue formation, which remains a major deficiency.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 9	• This group has enormous expertise in the field of SCI research. They have a great record of careful research to the highest standard. In this regard, everything is well planned. • The plans to move toward a banked NSC line for future clinical trials are solid. • This is a hard field. No matter what mechanism they propose, there is reason to push back and ask about another mechanism. On balance, however, this proposal addresses multiple necessary points. • There is no preliminary data from a spinal cord study to show that the polymer particles will tolerize the immune system to allogeneic NSC. Solving the immune rejection problem for NSCs is central to progress.
No: 2	• Good team. • Functional outcomes of limb function must be part of this.

	Is the score that will be derived in this set of experiments going to be relevant to humans?
GWG Votes	**Is the proposal feasible?**
Yes: 10	• The applicants can do everything that they propose. • There was interesting discussion on whether this fits better as a translational proposal or a discovery proposal. This is a difficult call, because this is a high-risk area of research. That said, one of the strengths of CIRM is the ability to take risks. • The experiments are feasible. However, the experiments as written do not lead to evidence that human lower arm and hand function is likely to be recovered. • The effect size in humans is likely to be much less than in animal studies. It seems unlikely the data from this will lead to a well informed clinical trial.
No: 1	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 9	• SCI is a major problem in underserved communities, but those injuries are often gunshot wounds. Such injuries are different from contusion injuries. Whether similar strategies can be used in both cases is unknown, but we don't have good animal models for gunshot-type injuries. • Fine for this translational stage application.
No: 2	• There is a description regarding being inclusive and that infrastructure will include a diversity of people, which is a strength. • Given costs, there may be better ways to help disadvantaged individuals with SCI. This research is not even remotely curative. It is by its nature incremental lacking clear mechanistic targets. • Not well addressed.

Application #	TRAN1-12891
Title (as written by the applicant)	Clinical Translation of Allogenic Regenerative Cell Therapy for White Matter Stroke and Vascular Dementia
Translational Candidate (as written by the applicant)	Human induced pluripotent stem cell (iPSC)-derived glial enriched progenitors
Area of Impact (as written by the applicant)	Vascular dementia and white matter stroke
Mechanism of Action (as written by the applicant)	Preliminary *in vivo* efficacy studies indicate that our glial-enriched progenitors promote new connections in the brain after white matter stroke.
Unmet Medical Need (as written by the applicant)	Our candidate therapy delivers a stem cell-derived product that enables recovery in vascular dementia, a condition with no currently approved therapy.
Project Objective (as written by the applicant)	Pre-Investigational New Drug (IND) meeting with the Food and Drug Administration (FDA)
Major Proposed Activities (as written by the applicant)	• Pharmacology/Toxicology: Confirmatory *in vivo* pharmacology studies and pilot *in vivo* tumorigenicity study • Manufacturing: Cell therapy product generation, formulation and qualification of manufacturing process • Clinical/Regulatory: Development of clinical trial documents and preparation for pre-IND meeting
Statement of Benefit to California (as written by the applicant)	This research will develop a therapy for vascular dementia- a common, devastating disease with no treatment. The intellectual property for this therapy is held by a public university in California, and commercialization will directly benefit the State of California.
Funds Requested	$5,925,602
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All Grants Working Group (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	3
Highest	88
Lowest	80
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	7
(1-84): Not recommended for funding	7

KEY QUESTIONS AND COMMENTS

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

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 12	• White matter stroke comprises 30% of all strokes and currently there are no treatments. A product that treats treat white matter stroke would have significant impact. • The major strength of this proposal is that the applicants intend to use a unique cell population that they have developed and studied over the last decade. They have demonstrated that their cells impact both cognitive and motor defects in animal models of white matter stroke. The project is unique and highly significant. • Certainly a worthwhile indication. • The need for better therapies for treatment of white matter stroke, or for any kind of stroke, is enormous. Current therapies are of marginal value, and this application provides a promising new approach.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• The project is based on the sound rationale of using pro-reparative astrocytes in order to ameliorate damage to the central nervous system. • The applicants have developed a population of glial-enriched progenitors from induced pluripotent stem cells (iPSC) that show a positive impact on both cognitive and motor functions in animal models of white matter stroke. These glial-enriched progenitors have been produced from 5 independent iPSC lines - therefore the differentiation protocol is robust and should be applicable to other pluripotent cell lines. • The applicants have been responsive to reviewer feedback on their previous submission for this project. • Working out the appropriate human dose may be challenging. The applicants' basis for choosing a dose seems plausible but in the end the dose may be much higher. • The applicants' preliminary data show that multiple different sources of glial-enriched progenitors all improve motor outcomes in animal models after experimental stroke. Glial-enriched progenitors also improve cognitive function in animal models as measured by novel object recognition and fear conditioning. • The proposed use of 6-well trays is not practical. Multiple groups have worked on expansion conditions for glial precursor cells, and examination of spheroid growth, cell stacks and other growth conditions are strongly recommended. • It seems important to interact with the Good Manufacturing Practices (GMP) cell production labs in the CIRM portfolio to explore other expansion conditions.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 11	• I think most of the planning is appropriate. The first time this project was presented I had a lot of concerns about manufacturing; most of those concerns have been addressed in the resubmission. • The science is outstanding and a major strength. The unrealistic plan for cell expansion is the cardinal weakness. • The applicants have estimated the number of cells they will need to conduct their planned trial. The number does not appear to be correct. At 10 million cells/patient, with 20 subjects in a phase 1 and 70 patients in a phase 2, they will need to manufacture a minimum of 900 million cells. Assuming cell culture losses of about 10%, they will need about 1 billion cells. For a dose of 40 million cells/patient, they will need about 4 billion cells. In general the project is fairly well designed, but errors of this nature give me concerns about the careful planning of the project.
No: 1	• The manufacturing considerations for scale-up are serious issues.
GWG Votes	**Is the proposal feasible?**
Yes: 7	• In general I think the project is feasible, but changes are needed in the manufacturing plan. • Scale-up manufacturing remains a serious concern. There is an obvious need to add an experienced consultant/manufacturing collaborator.

	• For scale-up the applicants plan to increase the number of 6 well trays that they use for growing cells. That strategy is not realistic for a 35-day process that involves media changes on nearly a daily basis. Because a six well tray is an open vessel (you need to take the lid off to feed cells), there will be sterility issues with scaling. • It does not appear that the applicants have performed a careful workflow analysis for the differentiation. How many operators, how many hoods, and how many unit steps are needed? How long will it take to feed all of the plates each day (including media changes)? • This project is feasible if they solve the cell expansion problem. I think the likelihood of their doing this is high, but the conditions proposed are not going to prove practical for development of a product for clinical studies.
No: 5	• I was swayed by the discussion concerns about scale-up and cell numbers. They should revisit these areas and return with a better plan. • The big issue is the scale-up. Using 6 well plates for large scale manufacture is not feasible; they will need closed systems and/or bioreactors and have not addressed this. • The approach to rely on 6-well dishes for manufacturing scale-up is problematic. Likely it is possible to change the plan for cell culture systems, but this is not trivial and will require time. • If major manufacturing changes are needed, it could put IND-enabling studies at risk.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 12	• White matter stroke impacts all manner of people. I do believe the applicants have done their best to make sure underserved communities will be represented in the patient populations they choose. • Stroke is a problem in all populations, and treatment improvement will benefit people regardless of their community. • Yes. Underserved communities are at higher risk of stroke.
No: 0	*none*

Application #	TRAN1-12907
Title	Investigational New Drug (IND)-enabling studies of a wearable therapeutic device for cardiac regeneration after myocardial infarction (MI)
Translational Candidate (as written by the applicant)	The therapeutic candidate is a wearable injector formulated with our proprietary cardio-regenerative factor.
Area of Impact (as written by the applicant)	The targeted area of impact is to restore cardiac function and reduce progression to heart failure in patients after myocardial infarction.
Mechanism of Action (as written by the applicant)	Our proprietary cardio-regenerative factor activates the controlled proliferation of progenitor heart cells within the infarct zone. The candidate treatment increases animal survival, reduces the progression to heart failure, substantially reduces cardiac scar size, restores cardiac function to nearly pre-infarct levels, and stimulates the formation of new cardiomyocytes and blood vessels. All these effects are limited exclusively to the infarct zone, and no adverse effects have been detected.
Unmet Medical Need (as written by the applicant)	Heart failure is a growing unmet medical need, with an enormous economic and societal burden worldwide, and remains incurable. Only regenerative therapies address the root cause of cardiac dysfunction and progression to heart failure after myocardial infarction.
Project Objective (as written by the applicant)	Pre-IND dossier for the Food and Drug Administration (FDA)
Major Proposed Activities (as written by the applicant)	• Therapeutic factor production using a Good Manufacturing Practices (GMP)-compliant process • Good Laboratory Practices (GLP)-compliant dose efficacy and toxicity, including comorbidity • Studies of variations of effect by race and sex
Statement of Benefit to California (as written by the applicant)	Heart disease is still the leading cause of death in California, accounting for 23% of all deaths. 62,797 Californians died of heart disease in 2017 compared to 16,355 who died of stroke. The proposed cardio-regenerative therapy will reduce death and disability of California's citizens who experience myocardial infarction, and reduce post-myocardial infarction progression to heart failure. The state will also benefit from lower health care costs and preserved productivity of Californians with heart disease.
Funds Requested	$3,923,191
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All Grants Working Group (GWG) members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 83

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

Mean	83
Median	83
Standard Deviation	4
Highest	90
Lowest	78
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	6*
(1-84): Not recommended for funding	7

* See Minority Report below

KEY QUESTIONS AND COMMENTS

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GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 11	• Strengths of the proposal include preliminary studies showing that the therapy promotes cardiac regeneration after myocardial infarction (MI) in small and large animal models. This therapy is unlike any other currently being studied in clinical trials. • Improving cardiomycocyte proliferation after MI would have meaningful impact. There is currently no treatment that improves cardiac cell viability/volume.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 11	• The applicants included many studies in order to submit an INTERACT to the FDA. They have also secured appropriate partners for GLP, GMP grade materials, and the device.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 6	• Yes. However, once a pre-IND is submitted, the FDA may require a large number of additional large animal studies. It would be better to combine the pilot studies with the future FDA-mandated studies. Please rethink the number of groups and sample sizes in your plan for pilot studies. • The large animal studies could be more focused at the pre-IND stage. The 10 dose groups in the pilot studies will be underpowered. Why not instead study efficacy and toxicology in the same studies? • It is difficult to justify the applicants' efficacy threshold: 10% reduction in fibrous scarring and 10% increase in myocyte volume. Unfortunately, this relatively small benefit likely won't be sufficient in a cost / benefit analysis. • The planned toxicology study uses a single dose; this is not adequate. • Yes. However, the injector is still in development and may require high import duties, affecting total cost.
No: 5	• The dosing studies appear poorly designed and extremely costly. It should be straightforward for the applicants to redesign and resubmit. • Please reconsider the design of the large animal study to increase efficiency. • The plans for the large animal studies should be re-designed to be smaller and more focused on studies that might be needed for the pre-IND. • The initial two preclinical, large-animal studies involve almost no collection of safety data. Full clinical pathology should be done on the blood samples. A separate pharmacokinetic (PK) study is requested in the budget, but it is not clear why PK samples couldn't be collected in the efficacy studies as well. • The only histology samples mentioned for the large animal study are from the heart. The applicant should consider more tissues (e.g. injection site) to support the safety of the product and device component. • It is not clear why the third study in the diabetic models is necessary for a successful pre-IND meeting. More justification is needed for funding this study. • The application states "funding not requested" under the regulatory section, but also states that safety studies will be conducted in "multiple animal models." This plan should be better described and justified. • Although the application indicates "funding not requested" for regulatory studies, the budget spreadsheet lists two GLP toxicity studies. The justification for using the chosen species and the design of the studies should be included in the application. The applicant should also further explain the timing of the safety studies relative to the pre-IND meeting.

	• There are inconsistencies in the application regarding the level of GLP compliance in the animal studies, and why it is justified. For example, in the activity budget spreadsheet the large animal studies are listed as "GLP compliant" but it is not clear what this means, especially since so little safety data is being collected. • This is a novel application of an unapproved device and protein therapeutic. The regulatory strategy should be more clear about the plan for meeting regulatory requirements for the device component (even if biocompatibility studies are funded elsewhere) and what device data will be used for a successful pre-IND meeting.
GWG Votes	**Is the proposal feasible?**
Yes: 11	• Strengths: preliminary studies, planned work for INTERACT, appropriate grade material. Weakness: rethink the animal studies prior to pre-IND.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 11	• Yes, because MI disproportionately affects underserved communities. • The proposal discusses policies accounting for diversity among management staff. • The therapy, if successful, could benefit the Medicare patient population, wherein 50% of patients admitted to the hospital with MI die within 3 years of discharge.
No: 0	*none*

MINORITY REPORT

If an application receives a Final Score of 1-84 and 35% or more of the scientific members of the GWG recommend an application for funding, then a minority report is provided that summaries the perspective of those scientific members.

Reviewers who scored this application 85 or above noted the increasing burden of post-myocardial injection heart failure and the novelty of a regenerative, rather than ameliorative, therapeutic approach. These reviewers were also optimistic about the delivery by subcutaneous injection, noting that this approach may be practical, widely adoptable, paid for by Medicare, and require no additional physician training. Individual reviewers who scored 85 or above were also pleased with the preliminary studies, qualifications of the Principal Investigator, partnerships, appropriate grade material, and/or conduct of INTERACT. Extant concerns in this group included off-target effects of the biologic, and/or potential time delays in toxicity testing and/or development of the injection device.

Application #	TRAN1-12889
Title (as written by the applicant)	Optogenetic therapy for treating retinitis pigmentosa and other inherited retinal degenerations
Translational Candidate (as written by the applicant)	A viral gene therapy delivering a light sensitive gene to treat patients with advanced Retinitis Pigmentosa (RP).
Area of Impact (as written by the applicant)	Retinitis Pigmentosa (RP) is a genetic disease that causes retinal degeneration leading to near complete or complete blindness for most patients.
Mechanism of Action (as written by the applicant)	Our candidate gene therapy delivers a potent optogene with high sensitivity to incoming light, and high dynamic range. Our viral transgene has been shown to effectively target retinal neurons, where it delivers a powerful light-sensitive protein. Light activation of the protein delivered by the transgene results in a signal to the visual cortex of the brain.
Unmet Medical Need (as written by the applicant)	Our candidate gene therapy will be used to treat patients with advanced retinitis pigmentosa (RP) and other inherited retinal dystrophies (IRD). These patients currently have no approved treatment to restore visual function and improve their quality of daily life.
Project Objective (as written by the applicant)	Pre-Investigational New Drug (IND) meeting
Major Proposed Activities (as written by the applicant)	• Preclinical animal studies to evaluate dose, safety and biodistribution • Manufacturing process and analytical development followed by manufacture of a toxicology batch • Pre-IND meeting with the Food and Drug Administration (FDA)
Statement of Benefit to California (as written by the applicant)	Retinitis pigmentosa (RP) is a progressively debilitating disease which leads to blindness. Of the approximate 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 special living assistance and suffer from loss of financial independence. Our candidate gene therapy represents a potential breakthrough treatment for a high unmet medical need to improve quality of life for RP patients.
Funds Requested	$3,997,636
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All Grants Working Group (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	82
Median	80
Standard Deviation	3
Highest	90
Lowest	80
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	4
(1-84): Not recommended for funding	9

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: 11	• The applicant is developing an optogenetic gene therapy that has the potential to restore vision in patients with inherited blindness. This viral transgene is injected into the eye using an intravitreal approach where it diffuses from the vitreous humor into the retina and transduces primarily the retinal ganglion cells (RGC). The applicant's target indication is a heterogeneous group of genetic diseases that cause retinal degeneration leading to near or complete blindness for most patients. Over 100 genetic mutations are known to cause Retinitis Pigmentosa (RP) and all types of inheritance patterns are recognized. • This product is not a stem cell technology. It is a gene therapy targeting retinal cells. The aim is to regenerate retinal cells and make them functional, thereby improving vision in individuals with near or complete blindness. • There is a large unmet medical need in RP. The proposed product is not curative, but if it works, it would provide additional light sensing capabilities for patients which presumably would improve their quality of life. • These optogenetic therapies have been in the clinic and have proven efficacy in improving ambulatory vision. • Patients with severe RP could benefit from this type of approach. These optogenetic approaches have been used in the clinic with limited success. • Important disease area.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 11	• The work is based on sound science and research. The team has a history of successful drug/therapy development. Their prior gene therapy using an earlier version of the light-sensitive protein was in fact tested in the clinic. It was well-tolerated but had a minor safety signal. • The rationale is sound. Optogenetics represents an emerging field of study. Developing an ophthalamic gene therapy based on optogenetics principles is both scientifically and clinically promising. Channelrhodopsin (ChR) over-expression in the retina has proven effective in restoring blindness in certain mouse models. The applicant has spent effort to develop more light-sensitive ChRs. They have created a highly light-sensitive (1,000 times more light sensitive) and effective ChR mutant through mutagenesis of a recently discovered ChR variant. • Yes. Optogenetics is currently being used in many types of scientific investigations and applied clinical applications, including RP. • Yes; this is based on previous work with a less effective protein. • The applicant has summarized a battery of published and unpublished studies to support the rationale of advancing this candidate into the clinic. Overall, the data supports the advancement of the product into the clinic. However, I have a minor critique. The applicants show in figure 4 that candidate-treated mice achieved an average visual acuity of 0.22 cycles per degree (c/d), in comparison to value of 0.40 c/d in normally-sighted mice. There is no negative or vehicle control shown. What does visual acuity look like in mice that have been injected with a buffer control instead of the transgene? • There is no negative control in figure 4.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 6	• Yes, this is a well-constructed, quality program. The team should consider including immunogenicity studies in both their dose/range safety studies and large animal studies. Specifically, the applicant should look at eye inflammation and the presence of transgene-specific cytotoxic T-lymphocyte responses (CTL) following vector administration. These will be important datasets for the IND. I suggest repeating what other commercial retinal viral gene therapy programs have done.

	• If everything goes according to plan, the outlined program should lead to a constructive pre-IND meeting with the FDA. However, timelines for getting all the work done appear overly optimistic. • I have doubts that the FDA will allow studies using a mouse model for IND-enabling toxicity studies. Historically the FDA has required data from larger species that better represent the human eye for IND-enabling toxicity studies. The applicant proposes using a mouse model and a large animal model for these studies. If more animal studies are required these would delay the applicants' IND timeline. • The preclinical studies are doable but the subsequent work is not well planned or detailed. The Chemistry and Manufacturing Controls (CMC) and analytical work will most likely take longer, they most likely will not be able to use a mouse for Good Laboratory Practice (GLP) safety/toxicity studies, and the use of their chosen transgene is a risk. The timeline is based on expectations for success at every step.
No: 5	• The proposal needs a more realistic timeline and more thorough planning of safety studies. • The major issues in this grant are the planning and time allowed for Good Manufacturing Practices (GMP), and the risk of immunogenicity of the transgene. • The immunogenicity of the capsid needs to be considered and studied.
GWG Votes	**Is the proposal feasible?**
Yes: 6	• The proposed timelines appear to be compressed and dependent upon performance of external vendors, who may not be able to deliver the expected outputs in the timeframes described. • The viral species will carry immunogenic and inflammatory ocular safety risks. Other commercial efforts to use intravitreal injections of similar viral transgenes have had program-closing safety issues.
No: 5	• The plan for CMC is not carefully laid out in the proposal. I believe the applicant will face major challenges, including plasmid manufacturing and characterization of viral vector purity. Their current plan is to fully outsource CMC to a contractor. • The applicant has allocated one quarter in the Gantt Chart/Timeline to transgene GMP; this will likely take 6 to 9 months for full GMP and release. • The timelines need to be more evidence-based, and relevant data should be included in the proposal. • The safety of the vector will require careful assessment.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 10	• Yes. The applicant plans to conduct outreach to eye care centers within areas of low socioeconomic status (by zip code), and to prioritize outreach to providers serving the Medicare and Medicaid patient population. • The team has listed ways to make this therapy available to underserved communities. The approach is realistic and actionable. • The applicants have planned and designed adequate resources to address and account for issues related to race, ethnicity, sex, and gender diversity.
No: 1	*none*

Application #	TRAN1-12919
Title (as written by the applicant)	Pre-Clinical Development of a Gene Corrected Autologous Airway Stem Cell Therapy to Treat Cystic Fibrosis Sinus Disease
Translational Candidate (as written by the applicant)	Gene corrected autologous airway epithelial stem cells from patients with Cystic Fibrosis
Area of Impact (as written by the applicant)	The proposed studies provide an innovative stem cell based approach with gene correction to treat chronic sinusitis in Cystic Fibrosis (CF).
Mechanism of Action (as written by the applicant)	Corrected upper airway cells will produce differentiated epithelium with restored Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene function. This restored function will enable improved muco-ciliary clearance which will resolve chronic sinusitis in Cystic Fibrosis (CF) patients and dramatically improve quality of life.
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. Genome editing enabling the precise correction of CF-causing mutations in airway stem cells offers a durable autologous cell therapy to treat CF.
Project Objective (as written by the applicant)	Sufficient pre-clinical data for pre-Investigational New Drug (IND) meeting
Major Proposed Activities (as written by the applicant)	• Rodent studies to validate the potential of edited cell delivery into the sinus using fibrinogen scaffold • INTERACT meeting with FDA to review proposed safety/toxicology/tumorigenicity studies and efficacy studies. • Good Manufacturing Practices (GMP)-compliant scale-up of cell production and delivery vehicle; quantify genomic integrity and *in vivo* safety
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 that this disease inflicts.
Funds Requested	$5,667,733
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All Grants Working Group (GWG) members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 80

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

Mean	81
Median	80
Standard Deviation	2
Highest	84
Lowest	78
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: 11	• Cystic fibrosis (CF) remains an area of unmet clinical need. Modulator therapy is efficacious in many patients but there remains a large population of patients who have class 1 mutations or are unable to tolerate the modulators. • The major burden of disease is in the lung, not sinuses, but the application is to develop a gene corrective cell therapy for sinus disease. This will have comparatively little impact compared with a corrective therapy for lung disease. The lung disease is not addressed by the application and remains a long way off. • The upper airway offers reasonable experimental model potential for the lower airway and therefore may help develop this process. • Meets a large unmet need.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 10	• They show the gene-corrected epithelial cells can form a well-differentiated epithelial layer in vitro with intact function. • They show mouse upper airway cells expressing a fluorescent protein can engraft in rodents over 90 days and that rodent cells in a fibrinogen scaffold stay *in situ* for 60 days. Additionally, they show human cells with fluorescent proteins in a fibrinogen scaffold can engraft for 48 days. • The gene correction data appear good. The data for correcting upper airway basal epithelial cells with two mutations is absent from the preliminary data. The technique to correct and tag appears to be well established and robust in the upper airway cells, and the ability to grow the cells in lab to adequate numbers seems good. • Using basal airway epithelial cells as a progenitor cell to repopulate the airway with gene-corrected cells is a good idea. There remains no good evidence, however, that the lower airway can be repopulated with exogenous basal airway epithelium - this remains a major hurdle. • Yes, the data suggest this can be used for testing in upper airways. There are no data to support the possibility of engraftment in lower airways.
No: 2	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 3	*none*
No: 9	• Good safety studies described. • More careful consideration of the rodent studies are needed to inform the development path. • An INTERACT meeting is recommended to justify their claims about the utility of the animal studies. • Little of the reviewers' comments on experimental design from the previous review have been taken on board. • Infection is not addressed in the *in vivo* studies, though survival in the presence of antibiotics is discussed. This is a barrier to understanding how the cells will survive in a chronically infected environment. • The testing of scaffold components and the ability of cells to engraft in mice are discussed. There remains little discussion of anything other than engraftment. Investigators focus on engraftment rather than function, and state that function in animal models is not relevant. *Ex vivo* function will be assessed but will be subject to artifact changes in cell culture. • While the investigators justify their lack of use of animal models, the argument is not convincing. Modulators did not improve function in rodents, but this experiment is different. CF rodents have abnormal nasal potential difference. Getting intact CFTR

	protein expression in the nasal mucosa should alter nasal potential difference and has been shown in rodents with other CFTR gene therapy correction strategies. • Tag expression does not equate to a functional CFTR at the apical surface of a cell. Tag-expressing cells will be a mix of basal cells, intermediate cells, goblet cells, columnar ciliate and non-ciliated cells (only the latter two cell types will express apical CFTR protein, if gene expressed). Therefore, there is a need for functional studies, to confirm proof of concept that the protein can be produced in the right place and to help inform dose. • No explanation for why six donors are enough, or which mutations should be tested. • The applicant's reasons for their choice of donors for GMP manufacture is not discussed. Why not include more of the donors that are the least likely to respond to modulators, and therefore represent the main target population? • Timing of cell engraftment after the denudation process is not discussed, but has been shown in other engraftment studies in rodents to be important. • Targets for degree of coverage is now discussed, but it is unclear how they plan to link this to dose for a human trial.
GWG Votes	**Is the proposal feasible?**
Yes: 9	• Excellent team and track record. • INTERACT meeting planned - maybe it should come earlier in the timeline.
No: 3	• Functional studies in vivo should be included.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 10	• Well addressed in the revised submission. • No addressing of gender (women have more severe disease than men).
No: 2	• Sex/gender differences need to be explored.

Application #	TRAN1-13048
Title	Off-the-Shelf Natural Killer (NK) Cells Derived from Umbilical Cord Blood Stem Cells to Treat COVID-19
Translational Candidate (as written by the applicant)	Chimeric Antigen Receptor (CAR) NK T cells derived from umbilical cord blood stem cells
Area of Impact (as written by the applicant)	Scale up and manufacture
Mechanism of Action (as written by the applicant)	Angiotensin converting enzyme 2 (ACE2) CAR specifically binds to spike proteins on SARS-CoV-2-infected cells, leading to clearance of both infected cells and virus. Completion of the proposed study will help us develop a novel cell therapy in compliance with Food and Drug Administration (FDA) regulations for the treatment of COVID-19 and halting coronavirus spread. Our frozen "off-the-shelf" NK cells will enable broad application for any subsequent coronavirus for which viral entry is facilitated by the ACE2-spike interaction.
Unmet Medical Need (as written by the applicant)	The COVID-19 pandemic is continuing, with >4.4 million deaths as of August, 2021. We have developed off-the-shelf, ready-to-use NK T cells engineered to specifically kill virally infected cells, clear virus, and stop viral spread.
Project Objective (as written by the applicant)	Complete Pre-Investigational New Drug (IND) submission to the FDA and finalize IND plans
Major Proposed Activities (as written by the applicant)	• Manufacture Good Laboratory Practices (GLP)- or clinical-grade mACE2-CAR NK cells for completing Pre-IND submission and demonstrating the ability to scale up manufacturing • Assess the competency and specificity of meACE2-CAR-IL-15 NK cells in controlling SARS-CoV-2 infection, including efficacy, dosing, and toxicity • IND submission to the FDA
Statement of Benefit to California (as written by the applicant)	COVID-19 is continuing to spread, especially in California, at an alarming rate with no sign that the pandemic will end. The delta mutant makes it worse. Public health and economic consequences have been devastating. Some therapeutics and vaccines have been approved by the United States Food and Drug Administration (FDA), but there have been no approvals for cell therapy. Our frozen, off-the-shelf product can specifically kill virally-infected cells to stop viral spread, which is greatly needed in California. Our product can be ready for next coronavirus pandemic.
Funds Requested	$5,838,284
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All Grants Working Group (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	80
Median	80
Standard Deviation	5
Highest	85
Lowest	70
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	1
(1-84): Not recommended for funding	12

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 9	• There is currently an unmet medical need to treat severe forms of COVID-19 and address chronic issues. This product aims to develop genetically modified NK cells to improve patient outcomes. • There is an unmet need for efficacious therapies for patients with severe COVID-19 that will be addressed in this proposal using a SARS-CoV reactive CAR NK cell product. • This translational research proposal seeks to capitalize on the efficacy and safety of chimeric antigen receptor expressing natural killer cell based therapies advanced by this group and others in the oncology setting through the utilization of such an approach in treatment of patients with COVID-19. • A single NK product could be used in a variety of settings to treat severely ill patients. • The practicality (and accessibility) of treating severe COVID-19 patients with an engineered CAR NK cell is questionable. First and foremost, the assertion of a lympho-depletion conditioning step to facilitate the therapy (as used in cancer clinic) might be incompatible with the clinical setting. Second, use in severe COVID patients in whom hypoxia conditions and steroid-based therapies are present may undermine the function of the product. Third, there is insufficient evidence that therapeutic NK cells will not contribute to lung pathology with either on-target (antiviral) or off-target effects and this cannot be captured in the proposed experimental design.
No: 2	• I am not clear on the ability to treat severely ill patients with this engineered cell therapy. • Currently not a critical unmet clinical need.
GWG Votes	**Is the rationale sound?**
Yes: 8	• The concept of CAR NK cells for infection is sound. • There is promising, although early, pilot data. • The insertion of a suicide switch is novel but not discussed much in the proposal - it adds a potential safety angle but this isn't really addressed. • A NK CAR targeted to COVID-19 ACE2 receptor additionally expressing interleukin-15 (IL15) has good rationale to increase the longevity of these cells. The main question is whether infusion of NK CAR T cells will be able to address the symptomatic aspects of the disease. The literature is spotty in this regard and in some cases NK cells have been associated with disease progression. • The provided preliminary data are supportive of the approach. The data generally support the specificity of the cell product. However, I am surprised that the discriminatory effects of the product are not more pronounced in Figure 5B.
No: 3	• The general rationale for using a stem-cell-derived allogeneic off-the-shelf NK cell product is strong and thus far well-substantiated in the oncology space with some early phase 1 trial evidence in infectious disease. This approach offers a safe and effective therapeutic cell platform that can putatively be administered repeatedly to achieve viral control and ablation of disease activity. The absence of dose-limiting toxicities or evidence of worsening inflammation following application of non-engineered allogeneic NK cells to patients with COVID-19 was reported in a press release from a company at the end of last year. Thus, the re-application of the allogeneic stem-cell-derived CAR NK cell platform to COVID-19 is reasonable. • In contrast to these positives, the rationale for restoration of antiviral NK cell activity is somewhat flawed. The premise derives from dual concepts that NK cells are primarily an antiviral effector cell and that these cells go missing in COVID-19 patients. The latter is an observation based solely on enumeration of circulating NK cells without any consideration for NK cells in SARS-CoV-2 target tissues such as the lungs. Indeed, accumulating evidence suggests intense activation and tissue trafficking of NK cells that is associated with disease course, positions NK cells upstream of COVID-19 pathogenesis, and implicates NK cells in harmful lung fibrosis. Indeed, mouse models of numerous pulmonary infections (Respiratory Syncytial Virus, influenza) suggest potential harm from

	exuberant activity of NK cells within the lungs. Thus, the simplicity of a one-dimensional restoration of antiviral cytotoxic NK cell function in COVID-19 and associated design of interventional trials must include consideration of both beneficial and detrimental activity of the NK cells. ● Strong deference is given to safety data with application of non-engineered allogeneic NK cell products to patients with COVID. Notably, the trial with non-engineered allogeneic NK cells was designed to enroll dozens of patients with mild to moderate (not requiring intensive care support or mechanical ventilation) COVID-19, though ended up enrolling fewer than ten patients. Half of the four reported patients also received remdesivir or a combination of dexamethasone and convalescent plasma. Three patients recovered while a fourth progressed and succumbed, an outcome where a contribution of therapeutic NK cells could not be ruled out. This brings up several points in consideration of that trial as an exemplar for the present approach. First, potential safety warnings do exist within those trial data, though the trial is only designed to capture acute toxicities. The possibility of progressive lung dysfunction exacerbated by CAR NK cells would be difficult to distinguish from that caused by COVID-19 itself. Second, popular media reports and even scientific reports (in context of phase 1/2 expectations) of successful recovery after administration of such products is difficult to untangle from contributions of steroids or other standard of care treatments. Third, the targeting of moderate patients in those trials is incongruent with the proposed targeting of severely ill patients in this approach. ● The activity of NK CAR in an acutely infected patient may be different from what the applicants anticipate. ● A major issue that needs to be addressed is whether lympho-depletion is essential for the therapy to work, as it is likely to be problematic in COVID-19 patients. Also need greater attention to possible risks of NK cells in this patient population.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 8	● Very responsive to previous feedback. ● Overall the details of the program are well designed. ● The preliminary infection data are supportive although numbers in the ACE2 mouse/SARS-CoV-2 infection experiment were very small. They do demonstrate an antiviral effect (reduction in viral load) and reduced lung histological damage with the cells. ● I have some concerns about the modeling with immunodepletion - the preliminary data suggest ACE-NK cells will reduce viral load and improve survival but they show very high mortality in viral infected animals by day 6. How will this allow late testing at day 6 as is proposed in Milestone 5 (the survival data they plan this experiment were based on Figure 1 where there was no immunodepletion)? Immunodepletion also potentially will affect host response to the virus and some of the so called cytokine activation and inflammation that occurs in patients with COVID will not be modeled here if there are no lymphocytes or macrophages. ● Lymphoid and macrophage depletion is a limitation - the applicants will need to model the administration of cells in non-macrophage/lymphoid depletion animals. ● While lymphodepleting therapies are used for CAR products in cancer, it is unclear whether such regimens will be needed when targeting an infectious disease. The plan should include use of animal models that would more closely mimic the actual real circumstance of the clinical trial. The current animal models in Milestone 2 do not address this point. ● Yes, especially around the dose justification and the testing in the presence of other immunomodulatory therapy. However, those experiments are likely to be complicated and require careful statistical evaluation. ● There are power calculations now included, which suggests the sample sizes have been considered more now - although I found the rationale and treatment effect sizes anticipated a little hard to follow.
No: 3	● A major concern in the translatability of the existing data and proposed experiments is the artificial creation of leukopenia in their mouse model through depletion of NK cells, T cells, B cells, and myeloid cells. The rejection of allogeneic CAR T cells and the limited durability of donor cells in a lymphorepleted environment are currently major roadblocks to success in cancer therapy that are overcome through the use of chemotherapy/radiation to deplete recipient immune system. How will this pre-clinical environment be recreated in COVID-19 patients without use of similar lymphoablating therapies? Not only might this permit pre-clinical advancement of a product with no clear avenue to clinical use, but the absence of myeloid cells as major mediators of CAR cell

	cytokine-release and associated toxicities is sure to artificially skew the measured safety parameters away from those that would be achievable without lymphoablation in a COVID-19 patient. This same issue weakens the support for this proposal provided by the wealth of success by the PI in using stem-cell derived CAR NK cells in oncology, where preconditioning removal of the immune compartment is presently the rule. Finally, the lymphodepletion experimental strategy undermines the value of Milestone 6 in which the putative targets of anti-IL6R or steroid therapies are absent. ● The power calculations are based on comparison of protection (optimal dose CAR-NK cells) to lack thereof (saline or control NK), but the partial efficacy of control allogeneic NK cells (or suboptimal doses of CAR-NK) in Figure 7 with regards to viral control, survival, and pathology will complicate these analyses and interpretations. This is further complicated by switch to low dose in lymphodepleted hosts based on data in Figure 1 using lymphoreplete animals. ● Viral dose might still be problematic based on the data provided in Figure 1. Half of immunoreplete mice given this dose die by day 8 or 9, which: (1) may be exacerbated by the planned immunodepletion strategy, and (2) which may complicate ability to assess therapeutic benefit. Is this really indicative of the clinical setting since weight loss onset in the immunocompetent model is only apparent two days prior to death (onset day 6-8)? Are there other symptoms relevant to clinical parameters of COVID-19 patients that could be monitored to more precisely determine timing of therapeutic interventions? ● The pharmacology Milestone 3 experiment is in lymphoreplete mice in the absence of SARS-CoV-2 spike protein antigen. It is likely that donor cells will be rejected in this context and never activated (to cause any toxicity that would normally result).
GWG Votes	**Is the proposal feasible?**
Yes: 10	● The applicants are exceptionally experienced in development and testing of genetically engineered stem cell derived NK cell therapeutics. ● The timeline, benchmarks, and milestones are appropriate for the timeframe and ambitions of the proposal. ● Exceptional team. ● The team and program at the institution is well resourced. ● The contingency plans are satisfactory. ● Good team feasible but very ambitious experiments around testing with current standards of care. ● The caveats of this program are the untested issues associated with the use of NK cells in a COVID setting. The animal studies are limited that they do not use a lymphocompetent animal model which will be the case when translation into human clinical trials.
No: 1	● Unclear, as the potential need to condition patients prior to therapy may not be feasible in patients infected with COVID-19.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 11	● Yes, COVID-19 has hit minority and underserved communities very hard. This product and approach represents a new approach to limit mortality in this population. ● Yes. These are difficult to model in mice but gender is addressed. The plans for the next development steps and testing in humans address diversity. ● Yes, this product would be applicable where there was poor vaccine uptake, late presentation or severe disease, addressing many of the issues that have affected underserved communities. The cost of this product is anticipated to be low compared to other cellular products being tested for COVID-19. ● COVID-19 disproportionately affects undeserved populations, so such a therapy would address and account for influence of race, ethnicity, sex and gender diversity.
No: 0	*none*

Application #	TRAN1-12892
Title (as written by the applicant)	Targeting scar-forming progenitors with a novel small molecule to reduce surgical complications of total joint replacement surgeries
Translational Candidate (as written by the applicant)	A small molecule that prevents fibrosis of progenitor cells present in the joint
Area of Impact (as written by the applicant)	Arthrofibrosis, or joint pain and mobility limitations that often arise following joint replacement surgeries
Mechanism of Action (as written by the applicant)	Our candidate small molecule is designed to reduce the transition of progenitor cells in the joint to scar tissue following surgery. If this transformation can be reduced, patients will have less need for follow up procedures, fewer opioid prescriptions, and fewer reductions in their quality of life. We also believe our candidate could impact many other conditions for which fibrosis is an issue.
Unmet Medical Need (as written by the applicant)	Joint replacement is an effective way to improve quality of life for patients suffering from osteoarthritis or trauma. However, >10% of patients experience pain and loss of mobility after surgery due to arthrofibrosis. Our data indicate that our candidate could help these patients.
Project Objective (as written by the applicant)	Pre-Investigational New Drug (IND) meeting
Major Proposed Activities (as written by the applicant)	• Rodent studies defining how best to deliver our small molecule therapeutic candidate • Preliminary assessment of safety and toxicity of the candidate • Pre-IND meeting
Statement of Benefit to California (as written by the applicant)	Our study offers a strategy for preventing arthrofibrosis. Nearly 10% of the population in CA are uninsured and 16% have Medicaid. 50% of the population is of Hispanic or African American ethnicity, which is associated with more limited access to medical rehabilitation and higher susceptibility to arthrofibrosis after joint replacement. We seek to offer Californians a non-invasive, affordable option for arthrofibrosis risk reduction.
Funds Requested	$2,729,307
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All Grants Working Group (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	59
Median	60
Standard Deviation	7
Highest	70
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: 4	• The proposed product is aimed to address debilitating arthrofibrosis associated with total knee arthroplasty (TKA). • It could be impactful, but in a very small patient population. • It is unclear from the proposal how the drug candidate will be specific to the knee joint(s) and be free of side effects, which are observed in approved anti-fibrotic agents for pulmonary fibrosis.
No: 9	• The current proposal does not have the potential to make a relevant impact on clinical care within the given timeframe. • Arthrofibrosis affects 5-13% of patients undergoing total knee arthroplasty. This translates to 5-13% of the 70,000 patients in CA, or 3500 – 9100 patients in California annually who might benefit. • The Target Product Profile indicates that this therapeutic would be administered to all patients as a prophylactic measure to support recovery following TKA. It's not clear whether this would be seen as valuable, or be considered wasteful and/or redundant. • Two drugs for idiopathic pulmonary fibrosis are currently approved. • Monoclonal antibodies against the protein targeted by this candidate are already in development for fibrotic diseases. • An oral inhibitor of fibrosis (like this candidate) would be more attractive than the intra-articular injectable, but not clearly more efficacious than other oral anti-inflammatory options.
GWG Votes	**Is the rationale sound?**
Yes: 1	• The rationale for the discovery of novel anti-fibrotic drug candidates is sound. • Preliminary supportive data are presented in the application. However *in vivo* experiments were done in the lung fibrosis model, which may be misleading. • The mechanism of action of the proposed drug may be specific modulation of progenitor cells *in situ,* or it could be pleiotropic.
No: 12	• The rationale is supported by analysis of cytokine signaling in the arthrofibrosis disease process. However, some of the cited references are specific to cardiovascular disease or lung fibrosis. • The preliminary and preclinical data do not strongly support the rationale of this proposal. • There is limited efficacy data with the candidate, but there is preclinical data with an analog demonstrating reduced infiltration and reduced fibrosis. • The mouse model used to select the candidate molecule was a model of pulmonary fibrosis, yet there was limited discussion of the relevance of this model to arthrofibrosis. The animal studies also used intra-peritoneal (IP) administration of the candidate, so it is unclear what the efficacy might be with oral administration. • The applicants already have funding to develop this as a topical therapy. What is the justification for a systemic approach?
GWG Votes	**Is the proposal well planned and designed?**
Yes: 1	• The planning in this proposal is well presented and relevant. It remains uncertain, however, if this work could support a successful pre-IND meeting. The mitigation strategies and risk evaluation are inadequate.
No: 12	• No, because the model for systemic delivery was mouse pulmonary fibrosis. • No, because the mouse studies used IP administration but the applicants' plan is to use oral administration in the clinic. • It is not clear why there is a need to test the drug in both injection and oral routes in animals.

	• It seems that a pre-IND meeting could be held without the safety/pharmacology studies the applicants have proposed for late 2023 and early 2024. Are these studies part of a go-/no-go decision for this program? • The contingency plan and risk mitigation sections are not well-developed. • The applicants are currently conducting a trial with a similar candidate using injection. The preliminary results from that trial should guide the next steps for this proposed therapy.
GWG Votes	**Is the proposal feasible?**
Yes: 6	• The experiments would provide information relevant for next steps. Current concerns are an unknown risk profile for the patient group, and unknown risks of harms. • The proposal looks feasible.
No: 7	• The team identified a regulatory lead but a CV for this person was not provided to demonstrate relevant expertise. • There is very limited discussion of project risks. The only mitigation described was to select a different candidate if the current candidate shows poor bioavailability and/or safety in animals.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 9	• The applicant noted that members of underserved communities often have worse outcomes due to delayed treatment. It is not clear the proposed therapeutic approach will ameliorate this disparity.
No: 4	• The impact to underserved communities is overstated in this proposal. 95% of total knee replacement patients do well for 10 to 15 years. • Patients with arthrofibrosis are severely unhappy and represent an unmed medical need. However, it remains unclear if this sub-population can be clearly defined and if the applicants' approach would benefit this population.

Application #	TRAN1-13021
Title (as written by the applicant)	Exosomes to Facilitate Tissue Regeneration after Volumetric Muscle Loss
Translational Candidate (as written by the applicant)	Human allogeneic cardiosphere-derived exosomes
Area of Impact (as written by the applicant)	Skeletal muscle damaged sustained by major trauma such as motor vehicle accident, occupational injury, or gunshot wound.
Mechanism of Action (as written by the applicant)	The exosomes work by modulating the phenotype of immune cells such as monocytes/macrophages which consume the exosomes in the circulation, trafficking them to the injured muscle. There, exosome-exposed macrophages secrete paracrine factors which stimulate the endogenous muscle repair machinery to mount an effective repair response to regenerate muscle tissue damaged by volumetric muscle loss injury.
Unmet Medical Need (as written by the applicant)	Currently, there are no Food and Drug Administration (FDA)-approved therapies for volumetric muscle loss, leading to crippling loss of limb function and long-term disability. Our proposal seeks to use a biologic derived from heart progenitor cells to stimulate skeletal muscle repair machinery, which can become faulty after trauma.
Project Objective (as written by the applicant)	Pre-Investigational New Drug (IND) meeting
Major Proposed Activities (as written by the applicant)	• Dose optimization studies in rodents • Tissue distribution and safety studies in rodents • Large animal translational studies
Statement of Benefit to California (as written by the applicant)	No citizen of California is immune to extreme trauma caused by motor vehicle accidents. Such trauma is commonly associated with volumetric muscle loss - a crippling condition resulting in long-term disability. No FDA-approved treatment exists, and surgical reconstruction and physical therapy are arduous and costly. If our studies are successful, we may offer a solution to improve recovery and return the patient back to the workforce, relieving taxpayers of unemployment and disability costs.
Funds Requested	$5,386,117
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All Grants Working Group (GWG) members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 60

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

Mean	58
Median	60
Standard Deviation	6
Highest	70
Lowest	50
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: 3	*none*
No: 8	• Volumetric muscle loss (VML) arising from trauma is a big unmet medical need and there is no current approved therapy for restoration of muscle. • Repair of volumetric muscle loss (VML) from traumatic injury, e.g., car accidents, is a significant unmet medical need. However, the data presented do not indicate that the potential for impact for the specific exosome product is very great. • It is unclear how far this would accelerate the technology when the cardiosphere-derived cells (CDCs) have been tested for safety and efficacy in seven clinical trials already. • A lyophilized product that can be administered in the first two days after injury/VML would be a valuable tool to clinicians, if efficacy were good. • There is little evidence that the key cellular components of cardiospheres are actually stem cells - in which category I do not include the bulk of mesenchymal stromal cells. Similarly, the key cellular targets of whatever factor(s) in the exosome preparation may have regeneration-promoting activity have not been clearly identified, although these could include muscle stem cells.
GWG Votes	**Is the rationale sound?**
Yes: 1	• Yes, but the applicants need some more data to show that there is some effect of treatment on day 2 after injury. • Some mechanistic work is suggested. • The applicants present no clear data on the advantages of exosomes over parent cells.
No: 10	• The total body of data on recovery from VML promoted either by cardiosphere-derived cells (CDC) or CDC-derived exosomes remains quite limited. Extrapolation from other indications, such as the Duchenne muscular dystrophy mouse model and some of the results of ongoing human studies can be interpreted as favorable, but does not provide compelling evidence for the proposed translational program. • The data presented include only one figure (Figure 9) with directly relevant, strong evidence of therapeutic bioactivity of the proposed product. The main effect is an approximately 2 week acceleration of regain of muscle function with the exosomes versus vehicle - with the absolute difference sustained through week 6. However, the incremental improvements in function after week 2 appear the same in the vehicle versus the treated group. Whether that early acceleration will translate to a permanent quantitative benefit is not clear. In much of the stem cell literature in certain models (e.g., cardiac injury), similar early positive effects have not translated into sustained benefits sufficient for product registration. • Much of the application data is with CDC, and the applicant makes the case that the CDC data are relevant because the exosomes are the active principle of CDC. The application states that the exosomes "alone reproduce the efficacy of CDC in mice…" but the figure cited shows only exosomes versus vehicle, without comparison to CDCs. • The advantages for developing the exosomes over CDCs are logistical: enhanced stability, potentially superior immune tolerability, potentially easier for re-dosing. However, the data show that the exosomes produce the same efficacy as CDC in the mouse model of VML. This data therefore still leaves a critical question unanswered: How would the logistical advantages of the exosomes translate to better efficacy? There is no data showing a superior efficacy to CDC, which have been tried already in clinical trials. • Insufficient data provided to support rationale. • This resubmission contains additional data with a more defined proposed mechanism of action, which was lacking previously. However, the proposal still relies heavily on data with the CDC product rather than the exosomes. • The mechanism(s) by which the exosomes might promote regeneration remain poorly defined. The relative contributions of trophic factors, immunomodulatory factors, microRNAs, etc., potentially delivered in exosome preparations remain poorly understood. A significant role of monocytes/macrophages in their delivery is supported by the data

	presented, but this sheds little light on the mechanisms underlying the biological activities observed. As with mesenchymal stem cells, while there are abundant data showing potentially beneficial biological activities, progressing from that to an FDA-approved product still seems a long, uncertain road. ● The mechanisms of action are poorly developed.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 2	● No concerns.
No: 9	● The project design is not impressive, and not much improved since the previous submission of this application. The proposed dose-finding studies in the mouse don't actually address the issue of long-term recovery. The specific information to be gained and impact on product development of short term (one week) studies of "pro-inflammatory and fibrotic signaling" are not spelled out. ● Manufacturing is presented as if already fully accomplished. What still needs to be improved or validated? No rationale is given for such assays as qPCR expression profiling, IL-10 secretion, or an endothelial cell scratch assay. How can the VML-injured mouse study be used as a quality control/potency assay until it is clear what level of activity correlates with sustained significant benefit? ● While the assessment of efficacy and dosing regimen in the mouse model may be helpful, the design of the large animal study does not include collecting pilot data that might be important for pre-IND discussions (e.g. pilot biodistribution/excretion data, or pilot immunogenicity/safety data). ● Biodistribution and safety studies are described with methods, but the application provides little insight into what metrics would be used to guide go/no-go decisions, further product improvement, or better mechanistic understanding of the therapy. ● The large animal studies over 12 weeks again do not fully address the long term benefit of treatment, and shed no additional light on mechanisms of action. Furthermore, the investigators do not present clear go/no-go parameters for these studies with respect to further product development or, if needed, further optimization before entering clinical translation. ● The rationale for the large animal study is unclear. The application states that it is to “ensure therapeutic efficacy is not specific to mice” but there is no other justification for the sample size or how the study will support a successful pre-IND meeting. There do not appear to be endpoints in the large animal study beyond efficacy (dose-response investigations). ● The studies are planned sequentially and it is not clear why the mouse pilot safety studies in Activity 5 cannot be conducted in parallel with the large animal studies.
GWG Votes	**Is the proposal feasible?**
Yes: 4	● No concerns.
No: 7	● The milestones are presented qualitatively, so it is likely they will be "checked off" within the timeline. Whether that will generate a product that merits serious attention at a pre-IND meeting is hard to determine. ● The team is assembled exclusively of institutional personnel with a relatively inexperienced Principal Investigator, his mentor, a set of research associates, one postdoctoral fellow and one postdoctoral scientist. The FDA consultant has not yet been named. Evidence for experience in product development outside the academic medical center context is absent in the chart provided. ● It is good that there may be an FDA consultant on the project, but the person is listed as “to be named” and the application would benefit from earlier input from such a consultant, especially regarding the planning of animal studies (with a focus on successful FDA engagement). ● A large collaborative network is in place. However, despite having collaborators who are experts in the animal models, there appears to be a lack of expertise in design of preclinical studies and the type of data needed for a pre-IND meeting. ● Manufacturing plan is not adequate. ● It is unclear why there is a 14-month gap between the mouse studies in Activity 1 and 2 and the proposed mouse studies for Activity 5. The mouse studies in Activity 5 do not appear dependent on the studies in Activities 3 and 4. ● Most of the risks identified are related to the possibility that there will not be strong efficacy or dose-response data.

GWG Votes	Does the project serve the needs of underserved communities?
Yes: 5	• The team itself is impressively diverse. • The project plan does not address serving the needs of underserved minorities as a specific point in developing the plan. However, as noted in the application, the nature of the types of injuries to be treated would suggest that the individuals who might benefit from the proposed therapy would be fully representative of the diverse California population. Indeed, it might be skewed in some instances towards underserved racial/ethnic communities in which some of the types of injuries to be treated may be relatively more prevalent.
No: 6	• The application states that VML disproportionately affects members of disadvantaged populations. • Minimal development on prior Diversity, Equity and Inclusion response. • Insufficient plans.