APP #	TITLE	BUDGET REQ	FUND	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Resubmission	Previous CIRM Funding	Disease Indication	Product Type	Approach
TRANSLATION APPLICATIONS															
TRAN1-12245	Development of novel synNotch CART cell therapy in patients with recurrent EGFRvIII+ glioblastoma	**$2,663,144**	**Y**	**87**	87	3	79	90	12	2	N	N	Glioblastoma	Cell therapy	An autologous CAR T cell therapy that targets multiple antigens on glioblastoma tumor cells
TRAN1-12258	CAR-Tnm cell therapy for melanoma targeting TYRP-1	**$5,904,462**	**Y**	**85**	84	2	80	89	8	7	N	N	Melanoma	Cell therapy	An autologous CAR naïve/memory T cell therapy that targets a novel antigen TYRP-1 on melanoma tumor cells
TRAN1-12309	Pre-Clinical Development of a Gene Corrected Autologous Airway Stem Cell Therapy to Treat Cystic Fibrosis Sinus Disease	**$5,468,684**	**N**	**84**	83	3	80	87	6*	8	N	Y			
TRAN1-12250	HSC-Engineered Off-The-Shelf CAR-iNKT Cell Therapy for Multiple Myeloma	**$5,949,651**	**N**	**84**	83	4	75	88	2	13	Y	Y			
TRAN1-12287	Off-the-Shelf mACE2-CAR-IL-15 NK Cells Derived from Umbilical Cord Blood Stem Cells to Treat COVID-19	**$5,838,279**	**N**	**82**	83	3	75	88	6*	9	N	Y			
TRAN4-12428	Human iPSC-derived micro-heart muscles for high-throughput cardiac drug discovery	**$957,216**	**N**	**82**	80	7	65	88	6*	6	N	Y			
TRAN1-12388	Targeting stromal progenitors to prevent the development of heart failure after myocardial infarction	**$5,271,535**	**N**	**80**	81	4	75	86	6*	9	N	Y			
TRAN1-12322	Clinical Translation of Allogenic Regenerative Cell Therapy for White Matter Stroke and Vascular Dementia.	**$5,920,940**	**N**	**80**	78	7	60	88	3	12	N	Y			
TRAN1-12331	A human neural stem cell therapeutic candidate for the treatment of chronic cervical spinal cord injury	**$5,552,839**	**N**	**70**	74	5	70	83	0	15	N	Y			
TRAN1-12265	Exosomes to Facilitate Tissue Regeneration after Volumetric Muscle Loss	**$5,466,487**	**N**	**70**	68	5	60	75	0	15	N	Y			
TRAN1-12377	Neural Stem cell-mediated oncolytic immunotherapy for small cell lung cancer	**$5,088,499**	**N**	**-**	-	-	-	-	0	15	N	Y			
TRAN3-12427	Development of a novel, minimally invasive bone marrow harvesting device for obtaining stem cells from live donors and from organ donors.	**$1,443,942**	**N**	**-**	-	-	-	-	0	14	N	N			

*Qualify for Minority Report

Application #	TRAN1-12245
Title (as written by the applicant)	Development of novel synNotch CART cell therapy in patients with recurrent EGFRvIII+ glioblastoma
Translational Candidate (as written by the applicant)	Human T cells transduced with a lentiviral vector encoding anti-EGFRvIII synNotch-primed anti-EphA2/IL-13Rα2 chimeric antigen receptor.
Area of Impact (as written by the applicant)	Glioblastoma is the most common malignant brain tumor, affecting approximately 3 out of 100,000 people/year in the USA with extremely poor prognosis.
Mechanism of Action (as written by the applicant)	In our proposed system, the first antigen EGFRvIII, which is expressed exclusively but heterogenenously on glioblastoma cells, primes the T cells to induce expression of a CAR that recognizes EphA2 and IL-13Rα2, thereby eradicating glioblastoma cells expressing either EphA2 or IL-13α2. Efficacy was long-lasting and superior to conventional CART cells. The superb efficacy of these synNotch-CART cells was associated with excellent persistence (>100 days in vivo) and T stem memory cell phenotype.
Unmet Medical Need (as written by the applicant)	Glioblastoma is the most common malignant primary brain tumor, affecting approximately 3 out of 100,000 individuals/year in the USA. Despite surgical resection, radiation and chemotherapy, prognosis remains poor 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-IND application
Major Proposed Activities (as written by the applicant)	• Process development for manufacturing of EGFRvIII-primed EphA2/IL-13Rα2 CART 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 (SOPs)
Statement of Benefit to California (as written by the applicant)	Because the current California's population is nearly 40 million, approximately 1,200 people are likely to be diagnosed with this devastating disease every year. The institution has 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 forms of clinical therapy for patients in California.
Funds Requested	$2,663,144
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 87

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

Mean	87
Median	87
Standard Deviation	3
Highest	90
Lowest	79
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	12
(1-84): Not recommended for funding	2

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. 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: 14	• Glioblastoma (GBM) is a very deadly disease lacking effective treatment options. If successful, the proposed therapeutic candidate will address the unmet medical need in the therapy of GBM. • The proposed product aims to develop a new therapeutic option for Glioblastoma (GBM). There are no curative options for this disease. There is a tremendous unmet medical need for new therapies. • Major unmet need. • Highly innovative proposal. • GBM is a large unmet need. • A treatment is needed for this aggressive disease. • This product offers a significant value proposition for patients since there are no curative options for GBM patients. • For health care providers it may not have a significant value proposition because this therapy is still very complex and expensive. • Three of my major concerns are the heterogeneity of GBMs, including in EGFRvIII+ tumors, the widespread distribution of these tumors throughout the CNS, and the ability of intravenous delivery to adequately target the widely disseminated tumor cells.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 14	• The project is based on solid scientific rationale. It utilizes a recent advance in genetic engineering of CAR-T cells, which allows overcoming current challenges in therapeutic interventions for solid malignancies. • Yes, target heterogeneity is a major factor contributing to the low overall response rates for GBM that have been observed in the clinic to date. The proposed synNotch technology is being applied for the purpose of targeting multiple GBM antigens while avoiding potential on-target off-tumor safety issues. • The authors have published on an analogous concept, which uses a dual lentiviral transduction process to generate multi-target specific CAR-T cells for GBM. Specifically, the authors have show that T cells transduced with two vectors, one encoding the anti-EGFRvIII synNotch receptor, another encoding the inducible anti-EphA2/IL-13Rα2 CAR leads to selective killing of heterogenous GBM tumor samples and durable control of disease in xenograft mouse models. The dual transduced CAR-T product is an analog. To enable better feasibility and translation into the clinic, the authors generated a single lentiviral vector that encodes both α-EGFRvIII synNotch receptor and the inducible α-EphA2/IL-13Rα2 tandem CAR. This is the actual product that will be developed for the CIRM grant. Preliminary data, shown in Figure 6, suggests the actual product performs comparably to the analog product. • Targeting multiple antigens is attractive. • Triple targeting has a strong rationale in GBM. • Excellent technology used with 3 antigens targeted. On-target off-tumor activity is avoided because the three antigens all need to be expressed on the target cell. • The molecular biology of the synNotch system is interesting, and even elegant. But the rationale in terms of GBM biology is of concern. • Significant question about future clinical application - exclusively intravenous delivery, or should it be coupled with regional delivery to brain? • It is not clear what is the efficiency of trafficking of these CAR-T cells through blood-brain barrier. Would the number of target tissue-infiltrating CAR-T cells be enough to lyse the tumor? There is a risk of "too low therapeutic dose delivery" if only IV administration route is used. The discussion of IV vs. regional (intracerebral/intraventricular) is not settled in the field. I'd suggest comparing IV versus IV+IC/IV routes of administration in 2 groups of patients. • The applicants should evaluate the route of delivery as part of their pre-clinical studies. IV delivery alone may not be sufficient. I recommend the applicants look at IV vs regional delivery vs a combination of IV and regional delivery.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 14	• The project is well planned and designed. • Yes, overall the project is well planned and designed. The milestones and timelines are aggressive, but the team has a successful track record and the appropriate

	support from partners. Overall the project is well-constructed and has thought of the relevant studies that will enable a successful IND application for a first in human study. As noted above, the timeline appears aggressive, particularly with respect to the process development and GMP related activities. However, this is in line with CIRM's mission and demonstrates an appropriate level of urgency for this type of a project. ● The engineering strategy is cutting edge and supported by strong preliminary data. ● Yes, and they plan to evaluate the clinical trial vector properly. ● The project is strong with respect to the molecular biology, but not in regards to tumor biology. ● Should regional delivery of the cells be assessed? Consider concurrent IV and regional delivery. ● Consider intravenous+intracerebral arm.
No: 0	*none*
GWG Votes	Is the proposal feasible?
Yes: 13	● The milestones and timeline look reasonable. ● The team is great and has highly qualified personnel to conduct this type of studies. ● Yes, the team and their partners have a successful track record. The team appears to have a viable contingency plan and paths to managing risks and delays. ● The team and timeline are strong and well-positioned to complete the studies.
No: 1	● This is not clear. It's technically feasible, but whether it has relevance to treatment of real tumors is a matter of great concern.
GWG Votes	Does the project serve the needs of underserved communities?
Yes: 12	● Yes, the authors have considered a logical path for designing the project plan to adequately address the needs of underserved communities. If successful, this project would result in a therapy that would have broad application across the California population including underserved racial/ethnic communities. ● No concerns.
No: 2	● This will need more attention, just by virtue of the population of patients in the first group of interest. This will become less of a concern as time goes forward, as these tumors do not show an ethnicity or gender bias in any significant way. ● This is not well addressed in the project.

Application #	TRAN1-12258
Title (as written by the applicant)	CAR-Tnm cell therapy for melanoma targeting TYRP-1
Translational Candidate (as written by the applicant)	Autologous naive/memory progenitor T cells genetically modified to express a chimeric antigen receptor targeting the Tyrosinase-related protein 1
Area of Impact (as written by the applicant)	Patient with melanoma, without response or with relapse after immune checkpoint blockade therapy and patients with rare melanoma subtypes.
Mechanism of Action (as written by the applicant)	T cells genetically modified to express the 20D7SL CAR detect and kill melanoma cells with high expression of TYRP-1 (representing ~30% of all melanoma lesions). Our therapeutic candidate uses a subset of naïve/memory progenitor T cells (Tnm) with improved ability to engraft and reconstitute a functional memory response compared to fully differentiated T cells. We anticipate that using Tnm cells will lead to a potent and persistent anti-tumor response.
Unmet Medical Need (as written by the applicant)	Immune Checkpoint Blockade (ICB)-resistant melanoma is an unmet medical need. Despite the success of ICB therapy, 40% of patients with melanoma do not respond, and some responders develop acquired resistance. ICB-resistant melanoma frequency is higher in patients with rare subtypes of melanoma.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Optimize, implement, and validate the Therapeutic Candidate large-scale, GMP-compliant manufacturing and lot release criteria protocols • Assess safety (selectivity, reactivity in normal tissues, toxicology) and antitumor efficacy (cytotoxicity, cytokine release, tumor growth control). • Assess feasibility of enrolling patients with rare subtypes of melanoma in the clinical trial, draft clinical protocol and complete pre-IND meeting
Statement of Benefit to California (as written by the applicant)	In 2021, 11,450 Californians will be diagnosed with melanoma. Around 30% of all cases (3435) will present high levels of TYRP-1 and could potentially benefit from our therapeutic candidate. Acral and mucosal melanoma are subtypes of melanoma with higher expression of TYRP-1 and a much lower survival rate than cutaneous melanoma. Their incidence is higher in the Hispanic, Black, and Asian/Pacific Islander populations. This is especially relevant in California, given the diversity of our patients.
Funds Requested	$5,904,462
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 85

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

Mean	84
Median	85
Standard Deviation	2
Highest	89
Lowest	80
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	8

(1-84): Not recommended for funding	7

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. 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: 14	• Metastatic melanoma, refractory to the therapy by checkpoint inhibitors and other drug combinations has no effective and approved treatment options. The product candidate will likely impact an unmet medical need. • The TYRP-1 is an interesting and unique target for melanoma and developing CAR-T strategies could be highly impactful. Melanoma is a disease of high unmet need. • Broad impact for melanoma patients is unlikely, but the target patient population would likely benefit. • The authors are overestimating the market size and potential impact, because out of 30% of patients (~ 30k patients in US per year) with cutaneous melanoma, a highly expressing therapeutic target, a significant part will respond to first-line therapy - checkpoint inhibitors. Also, it is unclear how checkpoint inhibitors will impact TYRP-1 expression profile. • For better estimation of potential market size and value proposition, this product-candidate should also be compared with tumor-infiltrating lymphocytes (TILs). The indication is similar, but TIL product may be approved on the market next year.
No: 1	• Checkpoint therapies and TIL therapies have proven extremely effective in metastatic melanoma patients. The eligible population for this therapy would be melanoma patients that are refractory to TIL and checkpoint inhibitors. The percentage of melanoma patients that are refractory to the above listed therapies that have sufficient (TYRP-1) expression is surely lower than the number that they cite of ~30% of lesions.
GWG Votes	Is the rationale sound?
Yes: 15	• The rationale for the selection of a therapeutic target is sound. • The target and application are well chosen. • Use of CAR-T is a proven paradigm and the targeting of TYRP-1 on the cell surface of melanoma cells is a rational approach. There is a risk for de-pigmentation and targeting of the inner ear cells, but this is the risk of running a clinical trial in the future to determine the significance of such potential targeting. • The rationale to select naive/memory subpopulations of T-cells is not supported by the data, utilizing models, specific to the proposal. The authors make an assumption that selection for naive/memory T-cells will always be beneficial for the product potency and persistence. But the high manufacturing cost of such a selection step should also be considered. • The rationale is sound but the overall impact of this product is unclear.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 12	• The project is appropriately designed and well constructed. • The overall project plan is sufficient. However, there are critical studies that need to be performed to validate the safety of this target. Specifically, it seems they wait too long to assess TYRP-1 expression in normal tissues. They wait 7 to 18 months into their study plans to assess this issue. This seems like a major criteria for proceeding with the development plan that should be considered earlier in the process. • The manufacturing plan needs more work. • Manufacturing plan is underdeveloped.
No: 3	• The studies are well designed overall. The manufacturing component is a huge deficiency. There is no substantive data that they can manufacture the product. They are not using a proven method to make CAR-T cells - isolating CD62L cells is still investigative and there are methods available that enrich for naive and central memory T cells without specific CD62L cells. They need to show robust manufacturing. The target

	is expressed at lower percentages than indicated in the patient population that would be enrolled in the trial. ● Manufacturing is under-developed and too complex. ● Data on naive T cell enrichment needs to be provided. ● The ocular toxicity needs more evaluation in the retina.
GWG Votes	Is the proposal feasible?
Yes: 15	● The proposal is feasible. ● The timeline of milestones looks reasonable. ● The team is qualified and has experience with multiple similar translational projects and clinical trials in the past. ● The contingency plan, potential pitfalls, and management of possible delay are poorly written. ● The data sharing plan is good. ● Retinal toxicity should be monitored carefully.
No: 0	*none*
GWG Votes	Does the project serve the needs of underserved communities?
Yes: 15	● Nice description of incidence in underserved communities. ● Yes.
No: 0	*none*

Application #	TRAN1-12309
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 (CF)
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 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 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. CRISPR/Cas9 genome editing enabling the precise correction of CF causing mutations in airway stem cells offers a durable autologous cell therapy to treat CF.
Project Objective (as written by the applicant)	Sufficient pre-clinical data for pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Mouse 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. • GMP-like 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	$5,468,684
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 84

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

Mean	83
Median	84
Standard Deviation	3
Highest	87
Lowest	80
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	6*
(1-84): Not recommended for funding	8

*See Minority Report below

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. 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: 14	• Strengths include the overall technology platform and the proposal to use genome engineering and editing to generate a universal gene correction strategy. If this approach works, it would represent a novel therapeutic platform for CF patients. • A gene-corrected cell therapy could be curative for CF patients. • Potential for impact lies in the possibility of application to the CF lung.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 14	• The rationale is sound and the initial in vitro and in vivo data in NSG mice looks promising. • The mechanism of action is well established by the preliminary data. • Excellent background data with gene correction in the basal airway epithelial cell. Correcting CFTR function is demonstrated in using chamber experiments.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 10	• Yes, but there should be additional work and planning for the clinically-relevant animal models and other preclinical studies they will propose in the pre-IND meeting. There may be model development or preliminary data that is needed, and the sooner they start on it, the faster they may be able to enter the clinic. • More studies on the engraftment into a CF diseased environment (e.g., with pre-existing infection or mucosal layers) would be helpful. • Consider a large animal study and an in vitro study with infectious agents. • Lack of modeling infection is a concern. Will the cells survive in a CF sinus/nasal cavity to engraft and differentiate? This could be modeled in vitro and in vivo using mouse model of sinus disease and mouse UABCs, for example. • The focus on engraftment rather than function is a concern. I'd expect to see restoration of function in an in vivo CF model. • In general yes, but there were some issues with lack of functional studies. • Is there good rationale to proceed to creating GMP compatible standards/testing in phase 1 study of sinuses before knowing whether there is at least proof of concept that this might work in the lung/lower airways? Lower airway engraftment is not well established. It would be nice to know there was proof of principle the basal cells could engraft in a CF airway at least in small decided areas. Ultimately developing this technology for sinus disease is unlikely to have impact, and the value of the sinus experiments are in proceeding stepwise to lower airway therapy. • Dose justification is needed. Please discuss how the studies will inform a human dose of transplanted cells/mm2 denuded area, and the engraftment into dose for a phase 1 study. Please provide a justification of 20% restored cells being sufficient - does this not need a functional marker? • Provide more specificity on how and what data would be shared.
No: 4	• The applicants seem to be putting the cart before the horse. They are proposing to generate GMP grade material without having definitive proof of concept that the approach will work in a relevant animal model of CF, such as CF-/- mice or pigs. I recommend the authors consider proposing more clear pre-clinical animal studies that demonstrate clear therapeutic impact of their approach in relevant animal models of CF. • Better planning for the preclinical studies is needed. Consider species, models, and relevant endpoints that can then be shared with FDA.
GWG Votes	Is the proposal feasible?
Yes: 14	• The timeline and strategy are flexible enough to consider the FDA feedback. • Feasible.
No: 0	*none*
GWG Votes	Does the project serve the needs of underserved communities?
Yes: 11	• Partly addressed.
No: 3	• More specificity on how the product could serve the needs of underserved CA communities is needed. • This information was lacking in the proposal.

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 agreed that the universal approach of this project for a cell therapy with gene correction for cystic fibrosis would have an impact on patients with this disease. Reviewers thought that the preliminary data demonstrating the genome editing and implantation of cells in an injury model were strong, and the strategy of going after the upper airway would provide a strong foundation for further studies in the lung. The primary concerns of the reviewers centered around the models. The reviewers recommended functional animal studies instead of the engraftment focused studies, and recommended studies of the gene corrected cells in an infectious environment that would be more clinically relevant. Reviewers recommended completing the functional studies prior to GMP production. Reviewers also thought more detail on how the project could serve the needs of underserved communities was needed. Despite these concerns the reviewers thought that the engraftment data was promising enough to move forward with, and the team's prior experience with gene editing for another indication gave confidence to the project, and ultimately this group of reviewers scored the application in the recommended for funding range.

Application #	TRAN1-12250
Title (as written by the applicant)	HSC-Engineered Off-The-Shelf CAR-iNKT Cell Therapy for Multiple Myeloma
Translational Candidate (as written by the applicant)	Stem cell-based off-the-shelf CAR-iNKT cells
Area of Impact (as written by the applicant)	Multiple Myeloma (MM)
Mechanism of Action (as written by the applicant)	The proposed therapeutic candidate can directly kill MM tumor cells.
Unmet Medical Need (as written by the applicant)	MM remains an incurable disease, with a high relapse rate. The proposed therapeutic candidate can offer a new treatment opportunity for a broad base of MM patients.
Project Objective (as written by the applicant)	Pre-IND meeting with the FDA
Major Proposed Activities (as written by the applicant)	• Pharmacology study of the therapeutic candidate • Chemistry/Manufacturing/Control (CMC) study of the therapeutic candidate • Safety study of the therapeutic candidate
Statement of Benefit to California (as written by the applicant)	In 2021 alone, it is estimated that over 3,320 Californians will be diagnosed with MM, and over 1,250 Californians will die of this disease. MM results in devastating economic impacts to the state of California, in addition to the substantial economic and emotional impacts on individual patients and their families. The proposed therapeutic candidate can potentially become a life-saving treatment for MM patients and therefore benefit the state of California.
Funds Requested	$5,949,651
GWG Recommendation	(1-84): Not recommended for funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 84

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

Mean	83
Median	84
Standard Deviation	4
Highest	88
Lowest	75
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	2
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. 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	• Yes, although there are multiple cell based therapies with the same target in myeloma and a now an approved product. The potential advantage of the proposed solution is that it is allogeneic for HSC and may allow production of a more stable, better defined, consistent cell therapy product and will likely be cheaper. • The present proposal is a resubmission based on a previous application. The applicant proposes to develop an advanced HSC-engineered off-the-shelf allogeneic targeting CAR-iNKT cell therapy for multiple myeloma. Although there are many therapeutic options available for multiple myeloma, there remains a major unmet medical need for novel and potentially curative therapies. • Additional strategies for myeloma would be significant. • Multiple myeloma is a large unmet medical need.
No: 2	• There remains a clear unmet need for curative therapy for myeloma. • Unclear that this proposed product will compete effectively with multiple other chimeric antigen receptor-based products targeting the same antigen. Some are further ahead in development, and one has achieved FDA approval. • Despite the medical need, it was unclear how much of an additional impact this would have beyond what is currently available for similar targeting cell therapies.
GWG Votes	Is the rationale sound?
Yes: 12	• The major advantage of this approach would be the potential for triple targeting of the multiple myeloma cell. The major concern relates to the lack of data examining the impact of the product on primary multiple myeloma cells. Specifically, is the second target relevant in multiple myeloma patients, specifically late stage patients? If the applicants look at this issue, using primary cells from multiple myeloma patients, I would be willing to give a higher score worthy of funding by CIRM. • A weak "yes". The first target and the iNKT cell population for the second target seems potentially attractive, but supporting data as yet are not compelling. • A comparison against the now approved CART treatment needs further study. • There is concern about whether the first target remains a durable target in myeloma. The iNKT activity against the second target may bypass the risk of loss of first target, but may be lost as disease advances - this will be tested using patient derived myeloma samples.
No: 2	• It is not clear whether the two selected targets can improve efficacy in myeloma. • It is not clear if the dual targeting approach will help in cases of antigen-escape.
GWG Votes	Is the proposal well planned and designed?
Yes: 11	• Yes, the applicants have put together a well planned project plan and addressed the issues raised at previous submission. • Yes for the stated goal. However, it would be important to know the relative impact of the product against other approaches that are now approved. • Clarity of the equivalence or superiority over the existing approved product would be needed.
No: 3	• Insertional mutagenesis in HSCs should be covered. • Shedding of one target and modification of the second target expression during MM disease progression needs to be addressed. • The data sharing plan is inadequate, it would be more worthwhile to fund this if the outcomes were publicly available in a well-defined plan.
GWG Votes	Is the proposal feasible?
Yes: 14	• The project plan appears feasible. • Good team and industry support. • The applicants have adequately made contingency plans for sourcing the cord blood units and the viral vector. However, a major risk factor with this program involves the potential for lentivirus insertional mutagenesis in the HSCs. The authors should develop additional contingencies in case they observe lentivirus insertion in oncogenic hotspots, which could put their program in jeopardy. • The platform has not been de-risked. • The data sharing plan was non-responsive.
No: 0	*none*
GWG Votes	Does the project serve the needs of underserved communities?
Yes: 13	• Yes, the iNKT cell therapy described in this proposal does not require matching between diverse polymorphic HLA haplotypes. If successful, the proposed iNKT cell adoptive cell therapy can be applied to treat all MM patients regardless of race/HLA restrictions. • The inclusion of underserved communities is described and appropriate.
No: 1	• This is only slightly addressed in the application.

Application #	TRAN1-12287
Title (as written by the applicant)	Off-the-Shelf mACE2-CAR-IL-15 NK Cells Derived from Umbilical Cord Blood Stem Cells to Treat COVID-19
Translational Candidate (as written by the applicant)	mACE2-CAR-IL-15 NK cells derived from umbilical cord blood stem cells
Area of Impact (as written by the applicant)	Scale-up and manufacturing
Mechanism of Action (as written by the applicant)	mACE2-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 FDA regulations for the treatment of COVID-19 and stop coronavirus spread. Our frozen "off-the-shelf" mACE2-CAR-IL-15 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)	SARS-CoV-2 is responsible for the COVID-19 pandemic and over 2.4 million deaths. We developed off-the-shelf, ready to use natural killer (NK) cells engineered to express the virus receptor ACE2 so that infused cells can specifically kill virally infected cells, clear virus, and stop viral spread.
Project Objective (as written by the applicant)	Complete Pre-IND submission and finalize IND plans
Major Proposed Activities (as written by the applicant)	• Assess the competency and specificity of meACE2-CAR-IL-15 NK cells in clearing SARS-CoV-2 and suppressing disease in vitro • Assess the competency and specificity of meACE2-CAR-IL-15 NK cells in clearing SARS-CoV-2 and suppressing disease in vivo • Manufacture a GLP or clinical grade meACE2-CAR-IL-15 NK cells for completing Pre-IND submission and demonstrate the ability to scale up manufacturing
Statement of Benefit to California (as written by the applicant)	Infections caused by SARS-CoV-2 are continuing to spread, especially in CA at an alarming rate with no sign that the pandemic will end soon. Public health and economic consequences have been devastating. Although some therapeutics and vaccines have been approved by the U.S. FDA , there are no approvals for cell therapy-based therapeutics to fight the virus. Our frozen, off-the-shelf product can specifically kill virally infected cells to stop viral spread, which is greatly needed in CA.
Funds Requested	$5,838,279
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 82

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	82
Standard Deviation	3
Highest	88
Lowest	75
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	6*
(1-84): Not recommended for funding	9

*See Minority Report below

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. 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	• Therapies targeted to SARS-CoV-2 are a highly unmet medical need. The proposed product adds to the diverse products that would be available to treat patients with COVID-19. • These studies could inform NK cell treatment for other diseases. • Yes but not for some time. It may have impact for other infectious diseases going forward as proof of concept for viral infections. • The NK cells are derived from umbilical cord blood stem cells, therefore yes. • As an alternative treatment approach, yes. However, it is not clear where in the current treatment paradigm the product would serve and whether this would be adequately modeled in the proposed studies.
No: 2	• I think there is some opportunity although this is a challenge given the time needed for clinical trials and the regulatory process. They should more carefully define how this fits into the course of care and whether this is to be used as a last-option agent, as that will affect their models and trial design. • The major concern of this application is that they don't actually demonstrate therapeutic benefit of their lead candidate mACE2-CAR-IL-15 NK cells. In Figure 7, the authors only look at difference in body weight between the experimental and control arm. There is no evidence that the mACE2-CAR-IL-15 NK cells actually lead to increased survival or control of viral load.
GWG Votes	Is the rationale sound?
Yes: 14	• Yes - a new NK cell-based therapy could assist with COVID-19 treatment. • Good rationale and excellent pilot data. • Overall, the scientific/clinical basis is sound. It is known that COVID-19 patients are deficient in T cell/NK cell responses, and a NK-IL15-CAR aims to address this deficiency. • The data presented is OK, but I would hope for much better effects. Most concerning is the animal models used are not typical for evaluation of therapeutics against SARS-CoV-2. The investigators spend much time justifying the model, but no viral titer inhibition data was presented. Body weights was the only data presented.
No: 1	• The rationale of the therapeutic product is sound. However, the pre-clinical evidence presented in the proposal does not demonstrate that mACE2-CAR-IL-15 NK cells can actually control COVID-19 infection and mortality in a meaningful way.
GWG Votes	Is the proposal well planned and designed?
Yes: 9	• Yes.

No: 6	• The pre-clinical studies are incomplete. There need to be additional proof of concept studies that address the actual ability of mACE2-CAR-IL-15 NK cells to control viral load and mortality in the pre-clinical humanized mouse model of COVID-19.
	• The application would benefit from a re-design of the animal studies to ensure proper models and dosing approach is evaluated.
	• The major issues are with the animal efficacy studies.
	  ◦ The viral inoculum is too high - most animals inoculated with this dose in the pilot data had died at day 7; even if the NK cells have excellent activity against the virus the controls will all have died within a week.
	  ◦ Viremia detected by PCR is of questionable relevance and doesn't differentiate live and dead bacteria. Live viral load in lungs at the listed time points (day 4/7 etc..) is more relevant than viremia.
	  ◦ Understanding the cytokine response in this model would be important even if there are some limitations in adaptive immunity.
	• Inoculum is too severe and not correct.
	• Concerns about the mouse model lacking human inflammatory mechanisms.
	• It is not clear at what stage of the disease process this treatment needs to be administered. This is critical for the treatment of an infectious diseases. Timing will be critical and the study design does not take that into account.
	• The investigators should consider how this therapy would work in the presence of corticosteroids which are part of standard care for COVID-19 infection in those hospitalized with pneumonia (and likewise in the presence of IL-6 inhibitors).
	• A general grantsmanship comment - sample size justification, consideration that the proposed numbers will have power to address both the primary and secondary outcome measures for the given experiment, proposed statistical analysis plans are all missing.

GWG Votes	Is the proposal feasible?
Yes: 15	• From a CMC and scale-up perspective, the proposal is feasible.

	The applicants have deep experience in the development of umbilical cord derived NK cells for therapeutic applications. ● The staff is well qualified and the timeline is appropriate. ● The team and environment are excellent.
No: 0	*none*
GWG Votes	Does the project serve the needs of underserved communities?
Yes: 15	● Yes, COVID-19 has significantly affected minority and underserved communities. This therapeutic product represents a novel intervention that may enable a new path for controlling COVID related morbidity and mortality. ● COVID-19 disproportionately strikes underserved communities so this therapeutic could serve those communities. ● The investigators describe a plan to serve undeserved communities. ● Potentially.
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.

Overall, reviewers agreed that COVID-19 is a high unmet need, and additional treatments such as the proposed product are important to develop. Reviewers agreed that the rationale is strong: NK cells are known to have antiviral properties, and there have been other successes with CAR NK cells including preliminary data provided by this group. Reviewers thought that the investigators' team was very strong, the proposed external advisory panel was valuable, and the product addressed the needs of underserved communities with an off-the-shelf product. The primary concern of reviewers was the limited evidence provided that the treatment can impact disease. The reviewers would like to see data demonstrating the product can reduce the amount of virus and not just impact animal body weight. There was also some concern that the proposed models would not accurately reflect human immune responses. Despite these concerns, these reviewers thought that this project would be important in building knowledge of CAR NK treatments for infectious disease, and potentially provide proof of concept for this approach, whether it was for SARS-COV-2, a variant, or another infectious disease, and ultimately this group of reviewers scored the application in the recommended for funding range.

Application #	TRAN4-12428
Title (as written by the applicant)	Human 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 2D 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 a FDA-approved compound library. • Test 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 heart muscle model enables normal heart muscle function for the faster and more effective identification of new drugs to treat heart failure, which would be an enormous benefit for the healthcare of Californians.
Funds Requested	$957,216
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 82

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	82
Standard Deviation	7
Highest	88
Lowest	65
Count	12
(85-100): Exceptional merit and warrants funding, if funds are available	6*
(1-84): Not recommended for funding	6

*See Minority Report below

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?

Yes: 8	• The proposed commercial development of a micro-heart muscle array likely will have a significant impact on an unmet need, that being having a system for drug discovery and high-throughput screening (HTS). • Could be a useful tool for cardiac drug discovery, which could help address a major unmet need. • The project would expand the use of hPSC derived cardiomyocytes in drug screening from 2D monolayers to more physiologic tissue-like constructs, accelerating development of drugs to treat cardiomyopathies. • Still at an early stage, and how to move from screening on normal cardiomyocytes to disease models isn't clear. • The timeline to realizing patient improvement is long even if this project is successful.
No: 3	• There is potential for significance but the research is still early stage (proof-of-concept). • There is no real clarity about how the product will be used. Will it be commercialized and would this not be needed for impact? This would be possible and important!
GWG Votes	Is the rationale sound?
Yes: 11	• 3D engineered heart tissues have been shown to better predict heart function than 2D cell monolayers but the manufacturing of these tissues is a challenge. The proposed project would enable the use of the 3D tissues in drug discovery. • The rationale is sound and the technology is interesting. • A 3D miniaturized system for screening on mature stem cell-derived cardiomyocytes is an attractive concept. • The proposed project is based on a sound scientific rationale. Although the PI has proposed a 3D in-vitro cardiac model to perform HTS for drug discovery, the PI needs to acknowledge the limitations of using this model in a HTS assay. There are limitations to this technology in drug discovery and drug predictability. • A precedent exists for using iPS cell-derived cardiomyocytes to understand cardiac toxicity. However, it is unclear exactly how the system proposed here for normal cardiomyocytes would be used to find new drugs for specific cardiac conditions. • The option to target compounds to phenotypes using this technology is exciting. Ultimately, I just don't really understand how this is going to be exploited/used and why it should be developed in this way unless it is to be used by wider community/at commercial level. • The commercialization plan is vague at this early stage.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 9	• The focus on transitioning to a multi-well screening platform is very clear and appropriate. • Integrated optical measurement of contractility and electrophysiology is an advantage. • Yes, the grant proposal is reasonable well planned and designed. • Focus on the engineering and achieving cost-effective high throughput system looks strong. • How the technology will incorporate cardiomyopathy disease models is unclear. • Need more on validation of system for actual drug discovery.
No: 2	• It is underdeveloped and still early stage.
GWG Votes	Is the proposal feasible?
Yes: 10	• The project is very technically sound and focused on developing a screening platform. • Yes, the proposal and the milestones outlined are feasible. • Cell biology and engineering seem feasible.
No: 1	• Uncertain.
GWG Votes	Does the project serve the needs of underserved communities?
Yes: 6	• Underserved communities experience heart disease, often at rates greater than average in the population. • Unfortunately the company doesn't have access to racially or ethnically diverse iPSC lines. This will be important moving forward.
No: 5	• The PI has not adequately addressed the needs of the underserved communities as it relates to this particular project. • The applicant needs to take into account more sourcing from various populations and the needs of diverse patient groups. • The description is very superficial.

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 agreed that this product could be a useful tool for identifying new treatments for heart disease. Reviewers thought that the 3D models, the technical aspects of the platform, and functionality focus were strong. However, reviewers thought that the project is still at early stages, and recommended demonstrating the tool could be used in disease models. Reviewers also thought the commercialization plan could be clarified, and could use more diverse cell lines to better reflect the patient population. Despite these concerns, reviewers thought the engineering aspects of the project were sound, the potential for this high throughput system to identify new drugs was appealing, and ultimately this group of reviewers scored the application in the recommended for funding range.

Application #	TRAN1-12388
Title (as written by the applicant)	Targeting stromal progenitors to prevent the development of heart failure after myocardial infarction
Translational Candidate (as written by the applicant)	Monoclonal antibody targeting Ectonucleotide phosphodiesterase/pyrophosphatase 1 (ENPP1)
Area of Impact (as written by the applicant)	Heart disease: To prevent the development of heart failure after heart attacks
Mechanism of Action (as written by the applicant)	After myocardial infarction, myofibroblast progenitors express ENPP1. ENPP1 is a type II transmembrane protein that hydrolyzes extracellular ATP and hydrolytic products generated by ENPP1 initiate an inflammatory cascade that worsens cardiac repair. The monoclonal antibody would bind to and inhibit ENPP1 on myofibroblast progenitors to decrease inflammation and scarring and augment heart repair and post injury heart function after myocardial infarction.
Unmet Medical Need (as written by the applicant)	Approximately 6 million people in the United States have heart failure (HF) and once a diagnosis of HF is made, approximately 50% survive 5 years. There is thus an unmet need for developing novel therapeutics for HF. The agent being developed will prevent the development of HF after heart attacks.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Development of a stable cell bank for antibody production • Rodent studies to determine dose • Development of biomarker to determine efficacy of therapy
Statement of Benefit to California (as written by the applicant)	Cardiovascular disease remains a leading cause of death in California and accounts for nearly one third of all deaths. The prevalence of heart disease is close to 25% in individuals above the age of 75 and 7% of individuals above the age of 65 suffer from heart failure. Heart attacks are the leading cause of heart failure and the therapeutic agent developed here will prevent the development of heart failure after heart attacks and of immense benefit to Californians.
Funds Requested	$5,271,535
GWG Recommendation	(1-84): Not recommended for funding

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	4
Highest	86
Lowest	75
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	6*
(1-84): Not recommended for funding	9

*See Minority Report below

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. 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: 14	• The prevention of cardiac scarring following myocardial infarction (MI) is an important unmet need. The successful development of an ENPP1 inhibitor could significantly improve patient care following myocardial infarction. • The disease focus is highly relevant. Ischemic heart failure contributes significantly to morbidity and mortality. • Therapies for heart failure is a large unmet need for CA residents. • Therapies to tackle the underlying mechanism of cardiac dysfunction would be of value across a range of cardiac disease processes. • There is a potential for the humanized monoclonal ENPP1 Ab to accelerate the development of a stem cell technology, but perhaps not in the area that the PI is suggesting. Post-MI, concerns remain about the potential for myocardial rupture by inhibiting the repair process. There may be a role of this product in other forms of cardiomyopathy that are associated with an increase in myocardial fibrosis.
No: 1	*none*
GWG Votes	Is the rationale sound?
Yes: 9	• The basic concept is to develop an inhibitory monoclonal antibody (mAb) for ENPP1 to decrease myofibroblast inflammatory activity and thus decrease heart injury and scarring, as well as increase healing. Literature data supports the approach of developing an inhibitory mAb for ENPP1 to improve outcomes after myocardial infarction. The initial data supports the approach of developing an inhibitory mAb for ENPP1 to improve outcomes after myocardial infarction. • The proposed experiments are based on strong preliminary data. • The mechanisms of action is well described and the role of the gene target in the overall disease progress is established. • There is strong preliminary data and mechanism of action. • There is concern about safety of inhibiting the repair process post MI due to risk of myocardial rupture (which is less common in mice than larger animals), particularly in the immediate post MI phase. The murine models are supportive but may not model human MI well. Inhibition of myocardial fibrosis with this drug might be better suited to other forms of heart failure, eg. hypertensive cardiomyopathy, sarcoidosis, rather than post MI.
No: 6	• I believe they need to refine their indication and then redesign the development plan to support it. • The rationale is sound but once again there is a concern about the administration of humanized monoclonal ENPP1 Ab immediately after a MI. Perhaps there will be a benefit a few weeks after a MI, or for other genetic forms of cardiomyopathy that are associated with myocardial fibrosis. • Two reviewers suggested there would be better rationale to develop this therapy for a different indication than immediate post-myocardial infarction. One raised safety as an issue for the specific indication. The other raised the difficulty of designing a clinical trial to show efficacy in light of generally improved outcomes after MI. Changing indication is a great deal to ask at this stage, but the concerns need to be addressed. • The rationale is not sound for the disease choice.
GWG Votes	Is the proposal well planned and designed?
Yes: 13	• Yes, the design of the study is reasonable. • The proposed experiments are a logical next step based on the preliminary data. The experiments are well designed. • The use of several models is to be commended but perhaps more could be done to address safety by using the large animal (porcine) model for efficacy studies with testing in those immediately re-vascularized and testing after an interval post MI. This would help give confidence that safety was being reviewed in appropriate model according to different times post MI/re-vascularization. • Chronic experiments in the mice and pigs need to be performed. • There is some concern that blocking or reducing the amount of fibrosis holds the risk of cardiac rupture. Similarly, the observation period is short and there might not be a longer term benefit. • The large animal study is over-designed. • With regard to study design, the pilot safety studies in the large animal model are over designed. It is proposed that they are conducted under GLP conditions and are currently designed as GLP first human dose enabling studies, not pilot dose range finding studies. For the pilot safety studies, it is good that bone safety will be evaluated and that the studies will be conducted at a known CRO.

	• The strategy behind the safety and pharmacokinetics package would benefit from input from an expert consultant. It is unclear what value a pre-IND meeting with FDA will bring to the design of the GLP first in human dose enabling studies. • Overall the project is well constructed, however, it can be improved by a more streamlined approach to first human dose enablement. The investigators could move more quickly to bring this therapy to the clinic. The development pathway and regulatory expectation for a mAb are well defined based on previous drug acceptance.
No: 2	*none*
GWG Votes	Is the proposal feasible?
Yes: 15	• The project is likely to be achieved within the proposed timeline. In fact, the project could be accelerated. • The proposal is feasible. • The team of investigators is well qualified to conduct the proposed experiments. Collaborators on this grant bring their unique strengths to the application.
No: 0	*none*
GWG Votes	Does the project serve the needs of underserved communities?
Yes: 13	• There are societal disparities associated with the treatment of myocardial infarctions as described in the application. • There is a significant and increased disease risk in minorities and underserved communities and this proposal can address that by improving treatment. • CA residents affected by heart failure could be served by this therapeutic.
No: 2	• There are some concerns about the PIs approach to the underserved communities. The majority of cardiomyopathies found in underserved communities is related to either hypertensive cardiomyopathy or other genetic forms of cardiomyopathy (ie sarcoidosis) and not primarily secondary to ischemic cardiomyopathy. The PI needs to understand more about these differences in the types of cardiomyopathies between different ethnic groups.

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 agreed that the successful development of a treatment that would prevent scarring after a heart attack would improve patient outcomes. Reviewers thought that the product had strong preliminary data, and the mechanisms of action were well described. However, reviewers thought that the proposed large animal studies are over-designed, and the chronic effects of the product need to be studied. Reviewers also thought there may be some risk to blocking fibrosis, as it may cause rupture. Despite these concerns, these reviewers thought that the team had strong collaborators, thought this treatment could benefit underserved communities who are disproportionately impacted by this disease, and ultimately this group of reviewers scored the application in the recommended for funding range.

Application #	TRAN1-12322
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-derived glial enriched progenitors
Area of Impact (as written by the applicant)	Vascular dementia and white matter stroke, addressing a current bottleneck of poor scale up for existing cell differentiation protocols.
Mechanism of Action (as written by the applicant)	Preliminary in vivo efficacy studies indicate that the mechanism of action is in the promotion of new connections in the brain after white matter stroke, termed axonal sprouting. Axonal sprouting is uniquely present in transplantation of hiPSC-GEPs, and not in transplantation of the precursor stage to hiPSC-GEPs, which is hiPSC-NPCs. Astrocytes promote the formation of new connections in the brain and axonal sprouting, by directly enhancing axonal growth and by promoting the synapses of these growing axons.
Unmet Medical Need (as written by the applicant)	There is no therapy for vascular dementia. The brain responds to this disease, and initiates a reparative response, but is blocked from fully engaging this response. This therapy addresses this condition by delivering a stem cell-derived product that enables recovery in vascular dementia.
Project Objective (as written by the applicant)	Pre-IND meeting with FDA
Major Proposed Activities (as written by the applicant)	• Pharmacology/Toxicology – Confirmatory in vivo pharmacology studies and pilot in vivo tumorigenicity study • CMC – Cell therapy product generation, formulation and qualification of manufacturing process • Clin/Reg- 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 a disease with no treatment, vascular dementia, that is common and devastating in its consequences. The intellectual property for this therapy is held by a public institution and commercialization will directly benefit the State of California.
Funds Requested	$5,920,940
GWG Recommendation	(1-84): Not recommended for funding

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	78
Median	80
Standard Deviation	7
Highest	88
Lowest	60
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	3
(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. 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:	• White matter stroke (WMS) and vascular dementia lack effective therapies.

14	• Yes - targeting white matter stroke is a novel and unique approach. • The applicants have developed a novel differentiation strategy for the production of Glial Enriched Progenitor Cells (GEP) from human pluripotent stem cells. • The focus on glial precursor cells able to generate pro-repairative astrocytes is a significant strength of the application. • It was not clear if the goal in transplants is to make only astrocytes or, in the white matter stroke, to also make oligodendrocytes. If so, what is then data on in vivo differentiation?
No: 1	*none*
GWG Votes	Is the rationale sound?
Yes: 14	• The fact that GEP could impact WMS symptoms is an exciting prospect so I do think this project is worth doing. • The focus on glial precursor cells makes a great deal of sense. • The preliminary data and mechanistic studies provide a strong rationale for this proposal with sound pilot data. • Transplanting these cells into a rodent model of white matter stroke shows improvement of motor skills compared to control animals. This rodent model can also address cognitive deficits and I would have liked to see experiments that address this point as many of the downstream consequences of WMS are cognitive in nature.
No: 1	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 6	• In terms of the glial cells and the in vivo use, the planning is great. • There are issues with the manufacturing process that need to be addressed. • A reviewer pointed out potential improvements in the manufacturing plan, but I believe these could be incorporated without need for resubmission. • Overall yes but there needs to be a review of the manufacturing process - consider creating biomass by expanding the early iPSC.
No: 9	• At a high level I believe the group needs help from a manufacturing expert to help them plan out the steps needed to make, bank and test a GMP master cell bank and working cell bank. That would be the basis for making product for definitive pre-clinical studies. • The manufacturing plan (e.g., making a master cell bank) is not strong enough to get into the clinic. • There is a lack of credible manufacturing plan. • The PI mentoring plan should be included given the inexperience with leading these types of projects. • The proposal is poorly written, and should be more thoroughly reviewed before re-submission.
GWG Votes	Is the proposal feasible?
Yes: 11	• Yes - excellent team. • Yes, I believe with the proper manufacturing help this project is very feasible. • The science is feasible, and the manufacturing plan needs to be improved. • PI insufficiently experienced, as evidenced by errors in the application.
No: 4	• The goals and milestones do not seem appropriate for the goal of a successful project.
GWG Votes	Does the project serve the needs of underserved communities?
Yes: 14	• Significant contribution to the development and promotion of scientist and future scientists as well as a dedication to medically underserved communities. • The injuries studied are a problem for all communities, and the generation of the banks that allow use in different populations is a positive. • Well addressed. • This will be more relevant when planning out clinical studies to address underserved communities.
No: 1	*none*

Application #	TRAN1-12331
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 GMP line developed under a prior CIRM award 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 FDA approved treatments for spinal cord injury. There are roughly 285,000 individuals living with paralysis due to traumatic spinal cord injury in the USA, with as many as 20,425 in California 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-IND and 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	$5,552,839
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 70

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

Mean	74
Median	70
Standard Deviation	5
Highest	83
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. 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	• Spinal cord injury (SCI) is devastating condition. Some biological therapies are in clinical trials but a cellular regeneration approach, if successful, would be of immense value. • The need for improvement in treatment of chronic SCI is great, and this group is one of the best at the pursuit of NSCs as a therapeutic option. • SCI is a large unmet need. • Relative merits of the proposed product versus other products in development remain to be seen.
No: 2	*none*
GWG Votes	Is the rationale sound?
Yes: 13	• There are multiple strengths in cell line characterization, and care of the studies. • Well-characterized starting cell population. • Absence of evidence for new tissue formation in prior studies represents a concern. • It would be of value to look at the protein expression for the markers they propose as predictive of outcomes. Looking at the proteins would also enable them to go after the one of the most vexing problems in this field, which is whether factors of interest are still expressed post-transplant, by immunostaining. • The mechanism of how demyelination could occur is not discussed. • Why are the applicants not assessing forelimb/paw function? This would be an important rodent equivalent measure to hand function in patients. • Use of a "standard" biomaterial known to generate toxic breakdown products and promote inflammation seems sub-optimal.
No: 2	• I'd like to see additional data validating the RNAseq potency assay, perhaps with another small animal model. Even better would be a transition to protein-based assay so it has a chance of more directly correlating. • The RNA screen will not necessarily inform clinical outcomes.
GWG Votes	Is the proposal well planned and designed?
Yes: 11	• The experiments are well planned, and the study of unbiased behavioral outcomes is a strength. This may benefit from more sophisticated statistical approaches. • Excellent design and attention to detail. • The adverse effects of the biomaterial in terms of driving foreign body reaction are not addressed but are important.
No: 4	*none*
GWG Votes	Is the proposal feasible?
Yes: 14	• If anyone can get something like this to work, this is the lab to do it. • The team would benefit from adding medical member(s) more experienced in treating spinal cord injury. • Need input from a chronic spinal cord injury specialist (eg. rehab physician).
No: 1	*none*
GWG Votes	Does the project serve the needs of underserved communities?
Yes: 14	• Nice commitment to underserved communities and the research community. • Significant contribution to the development and promotion of scientist and future scientists as well as a dedication to medically underserved communities. • These injuries affect all communities. One wonders, however, if the comparison with gunshot injuries is appropriate for a contusion injury model.
No: 1	*none*

Application #	TRAN1-12265
Title (as written by the applicant)	Exosomes to Facilitate Tissue Regeneration after Volumetric Muscle Loss
Translational Candidate (as written by the applicant)	Exosomes secreted by heart-derived progenitor cells (cardiosphere-derived cells; CDCs)
Area of Impact (as written by the applicant)	Skeletal muscle damaged sustained by major trauma such as motor vehicle accidents, occupational injury, or gunshot wounds.
Mechanism of Action (as written by the applicant)	CDC-exosomes, and by extension of CDCs (given they are the active principal of the cells themselves), work by modulating the immune system, suppressing fibrotic signaling, and stimulating the endogenous skeletal muscle repair machinery to regenerate tissue damaged by volumetric muscle loss.
Unmet Medical Need (as written by the applicant)	Currently, there are no 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 the muscle repair machinery, which becomes faulty after such trauma.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Rodent study to develop the optimal treatment strategy of the therapeutic candidate. • Rodent study to assess the safety profile of the therapeutic candidate. • Porcine study to translate efficacy from a small to large animal.
Statement of Benefit to California (as written by the applicant)	No citizen of California is immune to extremity 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	$5,466,487
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

Final Score: 70

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

Mean	68
Median	70
Standard Deviation	5
Highest	75
Lowest	60
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. 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	• Volumetric muscle loss (VML) is a major cause of long-term disability and poor quality of life in trauma patients.

	The applicant seeks to develop cardiosphere derived cell exosomes as a therapeutic to prime acutely injured tissue for regeneration and as an adjuvant to support continued recovery in trauma patients with associated VML. If successful, this approach has significant potential for impact. ● VML is an urgent need in CA. ● There is some potential for impact but as presented, there are major issues that reduce the enthusiasm for this application. ● There is strong potential, but the entire program could be at risk if it is determined that the therapy must be administered immediately after injury.
No: 4	● Significant unmet need. ● They have not provided enough information to show how they have addressed the issues with previous products that have yielded weak clinical results. ● Concern that essentially the same product, as well as the original live CDC material, has been tried in other regenerative medicine indications, with little evidence of efficacy. ● Mechanism of action of exosomes (as of the cells from which they derive) remains poorly defined.
GWG Votes	Is the rationale sound?
Yes: 7	● The preclinical data is encouraging and supports continued use and development of the CDC exosomes for VML. The mechanism of action of the product is a bit murky. Future studies should evaluate this. Some preliminary studies addressing the mechanism of action should be conducted and submitted with an application resubmission. ● There is some promising data from the animal model - when administered immediately, the exosome preparation appears to promote recovery of some muscle mass after volumetric muscle loss, with concomitant functional improvement. ● Concern that key component(s) delivered by exosomes are not identified, and basis of any regenerative effect remains unclear. ● The ability of the product to work across xenogeneic barriers (human exosomes into mice) is remarkable and not completely understood. In other settings exosomes are used to help promote immune activation by presenting antigens - for example, in production of certain cancer vaccines. One paper indicates PGE2 production by CDCs suppresses allogeneic lymphocytes. It is not clear whether the ability of the product to provide benefit in models across allogeneic or xenogeneic barriers is based on a similar mechanism, the absence of key target antigens, or some other property. ● While largely based on CDC work, there is some preliminary data with the exosomes, though it is only a small amount of proof of concept data in mice. ● Absence of more promising data from clinical trials of same or related products is a significant concern. What is the justification for going back to the well?
No: 8	● The rationale for using exosomes for the treatment of a condition like volumetric muscle loss is not as sound as for other progressive pathologies. ● The mechanism of action needs to be better defined and established. ● There are no positive clinical outcome data from the trials carried out to date in other muscle disorders using the cardio spheres. The rationale for why this would work now using the exosome preparation is unclear.
GWG Votes	Is the proposal well planned and designed?
Yes: 5	● Overall the proposal is well planned and designed.
No: 10	● Many of the milestones are stated qualitatively, more as specific aims than as quantifiable go/no-go steps towards development of a successful product. ● Milestones are not well planned. Among several issues, there is no information on quality control for exosomes (release criteria) and the idea of using lyophilized material is only superficially discussed. ● There are major concerns related to the quality control of the proposed exosomes. ● Not enough attention to manufacturing, especially for a lyophilized product. Ability to generate and validate reproducible batches isn't documented. ● No clear criteria or justification of what an adequate exosome preparation is and what the release criteria might be. ● Quality control of the product (e.g., release criteria) is not clear. ● The nature of the product seems ambiguous (e.g., lyophilized product). ● Relationship to the commercial entity is unclear - is that the source of cell banks & manufactured product, or are they being generated independently in the non-profit facilities? ● The window to treatment opportunity is risky. ● A resubmission with more preliminary data, specifically related to the 'treatment window' (activity 2) would make the approach more promising.

	• While the proposed experiments are important, some are 'over-designed' or could benefit from more careful planning. For example, it is great to add a second species (pig), but the dose-finding was not proposed in that species. • Porcine study appears poorly planned. Will be very challenging to get data on 48 animals in 18 weeks. No plans for dose/timing studies in the porcine model, where they would perhaps be more relevant than in the mouse. • Quantitative criteria for success in animal model that might be expected to translate to significant improvement for patients aren't clear. This is where more sophisticated muscle physiology and interaction with experienced rehab physicians would be particularly helpful. • The porcine model is underused to assess muscle function. • Large animal studies seem ambitious.
GWG Votes	Is the proposal feasible?
Yes: 12	• The proposal is feasible, however the timing of treatment remains unclear. The feasibility of administering the product in a translatable VML situation is a critical activity. The studies outlined in Activity 2, which aim to establish a window of opportunity for optimal tissue regeneration, are important to determine clear next steps and whether this product has a clear line of sight for VML. I suggest the applicants generate preliminary data that addresses the questions in Activity 2 and come back with a resubmission of this application. • The proposal is feasible. A major question is whether this treatment for VML is feasible considering treatment needs to be immediate. • Significant concern about the time window within which product must be administered to be effective. Mouse study addresses this, but pig study does not. • Future clinical trial and successful development of a product may be very difficult if time window within which product needs to be administered is too short. Merely getting informed consent within a short window after a potential trial subject has experienced a traumatic injury could prove very difficult. • Team would benefit from addition of physician(s) specialized in traumatic injury and rehab, as well as lab scientist(s) expert in skeletal muscle physiology. • PI appears a promising young investigator, but is still quite inexperienced to lead a translational project of this scope and will need a lot of mentoring. Some of this is reflected in weaknesses in the proposal. • The proposed experiments will drive the program towards a pre-IND, but there is no clear manufacturing plan for the exosomes.
No: 3	• Milestones are redundant and the go-no go decision needs to be clarified.
GWG Votes	Does the project serve the needs of underserved communities?
Yes: 14	• The application presented evidence for the impact of VML within underserved communities. • The applicants outline an adequate plan for addressing underserved communities. • This aspect was well-addressed. • Clear argument that underserved communities suffer disproportionately from the condition to be treated. • Diversity of the project team is presented nicely. • Potentially, given the stage of development.
No: 1	*none*

Application #	TRAN1-12377
Title (as written by the applicant)	Neural Stem cell-mediated oncolytic immunotherapy for small cell lung cancer
Translational Candidate (as written by the applicant)	A clinically tested tumor tropic neural stem cell (NSC) platform for effective distribution of oncolytic virotherapy to small cell lung cancer.
Area of Impact (as written by the applicant)	This NSC-delivered virotherapy approach will enable a more efficient, less toxic treatment for small cell lung cancer (SCLC) and chemoresistant cells.
Mechanism of Action (as written by the applicant)	LOAd703 is a replication-competent adenovirus with restricted replication and oncolysis to the dysfunctional retinoblastoma pathway, common in a wide spectrum of human tumors. We will use our tumor tropic/penetrating NSC platform to produce the oncolytic virus within SCLC. Viral replication will lyse cancer cells and infect neighboring cancer cells, thus amplifying its effect until reaching normal tissue. We will also stimulate a secondary immune response to newly exposed tumor antigens.
Unmet Medical Need (as written by the applicant)	Most SCLC patients present late stage with extrathoracic metastases, and can't complete chemotherapy due to severe toxicity and chemoresistance. NSCs will more effectively target and distribute an oncolytic virus, electively lysing cancer cells and stimulating an anti-tumor immune response.
Project Objective (as written by the applicant)	Pre-IND meeting, ready for GMP clinical lot
Major Proposed Activities (as written by the applicant)	• In vivo determination of dosing regimen (multiple rounds) for maximal therapeutic efficacy • In vivo determination of secondary immune response, following oncolysis of tumor cells • In vivo determination of preliminary safety/toxicity profile
Statement of Benefit to California (as written by the applicant)	Around 9,900 lung cancer patients are expected to die from lung cancer in California this year making it the deadliest cancer in California. SCLC is the most aggressive lung cancer with a dismal 6% 5-year survival rate. We anticipate that our stem cell-derived oncolytic virotherapy will lead to a more effective, less toxic treatment that will kill even metastatic foci and chemoresistant cells and improve the survival of SCLC patients in California
Funds Requested	$5,088,499
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

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

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

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. 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	• Small cell lung cancer (SCLC) is one of the deadliest cancers, with 34,323 new cases in the US in 2020 and only 10–20% 2-year survival. A conditionally replication-competent oncolytic adenovirus could have significant impact on patients with small cell lung cancer. Although this approach is technically complex, such a therapeutic approach has been demonstrated for other cancers. If the therapy performs as described, it will have significant impact for patients with SCLC. • This therapy addresses advanced SCLC that is difficult to treat. • Small cell lung cancer is extremely difficult to treat.
No: 6	• The patient population that they are going after is fairly small. • It's not clear how many patients in California would benefit from this therapy. • Limited applicability.
GWG Votes	Is the rationale sound?
Yes: 4	• The design of the project is sound and rational. However, some refinements should be made to aspects of the overall project. The currently available body of data supports the progress of the product to the next step.
No: 11	• The provided data are not convincing as to the potential of the product. • Major concern that the therapy is tested versus only one model human tumor-derived line that represents a minority of cases of SCLC. Efficacy in model not very impressive. • The pilot data are very weak, with missing controls, single replicates, and poor statistics. The cell line represents only probably <20% of the SCLC patient population subtypes of SCLC, therefore it is not particularly relevant to the wider patient group. • The preliminary data is extremely weak. • No evidence of benefit from the prior studies.
GWG Votes	Is the proposal well planned and designed?
Yes: 1	*none*
No: 14	• In general, the planned project meets the requirements for the development of a oncolytic virus therapy. However, the safety and biodistribution packages could use some improvement. A "common" approach to the assessment of oncolytic virus therapy is evaluation using tumor null mice and tumor bearing mice, as well as nonhuman primate species. There are plans in this project that include a pilot nonhuman primate study. Such a study would be useful for the pre-IND meeting. The mouse safety study is over-designed for a pilot study. Furthermore, the study is planned to be conducted under GLP which is not required. The pilot studies will be conducted in-house under GLP. With all respect to the investigators, GLP requirements are difficult to achieve for many institutes. The investigators should consider using a CRO experienced with this type of therapy to meet regulatory requirements. Biodistribution success criteria have not been well defined. • Major issues with preliminary data, poor choices of models for proposed studies, lack of any data with previous studies using NSCs. • The preliminary data is not based on a diversity of cell lines and cancer subtypes. • Controls are missing in the preliminary data. • The limited use of the single cell line is a concern.
GWG Votes	Is the proposal feasible?
Yes: 9	• The proposal is feasible. • A CRO should be used for future GLP safety studies.
No: 6	• The mention of GLP studies lacked explanation, both in rationale and proposed execution, suggesting a possible lack of understanding of GLP.
GWG Votes	Does the project serve the needs of underserved communities?
Yes: 9	• This was acceptable.
No: 6	• Not well defined in the application. • The eventual market seems small.

Application #	TRAN3-12427
Title (as written by the applicant)	Development of a novel, minimally invasive bone marrow harvesting device for obtaining stem cells from live donors and from organ donors.
Translational Candidate (as written by the applicant)	The device is a novel, minimally invasive device for the harvest of bone marrow, enabling use of marrow stem cells in multiple clinical settings
Area of Impact (as written by the applicant)	Addresses the need for rapid, minimally invasive harvest of bone marrow. Marrow derived stem cells are used in a widening array of curative therapies.
Mechanism of Action (as written by the applicant)	The device is a novel handheld, a powered medical device enabling the minimally invasive harvest of bone marrow. It employs an attached rotating flexible aspiration shaft that can move flexibly within the marrow cavity where bone marrow is aspirated under negative pressure via the shaft lumen and collected into a syringe or an aspiration canister. Higher numbers of marrow-derived stem cells can be collected.
Unmet Medical Need (as written by the applicant)	The device is a solution to meet the medical demand for BM-derived stem cells to treat a multitude of life-threatening medical conditions & create a pathway to provide BM-derived hematopoietic stem cell transplantation to confer immune tolerance following solid organ transplants (SOT).
Project Objective (as written by the applicant)	Readiness for transfer to manufacturing
Major Proposed Activities (as written by the applicant)	• Prototype and test efficiency and yield of device Gen-2A against standard marrow harvest approaches in live donors and deceased organ donors. • Prototype and test efficiency and yield of device Gen-e against standard methods for each donor type. • Develop integrated Marrow Collection System, and create optimized clinical and training protocols for use of the device in each donor type
Statement of Benefit to California (as written by the applicant)	This research will enable much easier access for bone-marrow-derived stem cell harvests used in bone marrow transplants, orthopedics, & regenerative medicine applications as well as research in California hospitals and scientific institutions. California marrow donors and hospitals will benefit from a less invasive donation procedure, and recipients of solid organ transplants in California will have the opportunity to achieve lifelong immune tolerance with newly enabled stem cell transplants.
Funds Requested	$1,443,942
GWG Recommendation	(1-84): Not recommended for funding

SCORING DATA

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

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

KEY QUESTIONS AND COMMENTS

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GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 2	• More access to bone marrow (BM) with less pain could be useful. • Possible impact but without additional data it is not clear if there is improved content, utility.
No: 12	• The applicant seeks to develop a prototype device to enable rapid and minimally invasive harvest and collection of BM for autologous or allogeneic use. Current standard of care seems to be sufficient for BM harvests/aspiration. This device doesn't have a significant potential for impact to increase the reproducibility and yield of BM harvests. • Not clear this addresses a significantly important unmet need. • It's unclear that the modifications to the existing device will have substantial impact. • The impact is unclear.
GWG Votes	Is the rationale sound?
Yes: 1	*none*
No: 13	• The goals do not appear to have well-defined endpoints. What improvements will these interactions make to the bottom line and how will these improvements be measured? How will these improve stem cell yield? • A true need for the device and evidence of benefit needs to be demonstrated. • The most substantive data in this proposal, summary of device Gen-1 harvests in human trial, does not show a significant increase in total nucleated cells compared to current standard of care. Likewise, it's unclear what cell types they are harvesting and how it compares to standard of care. Are they getting an increased yield of CD34+ cells compared to standard of care? The applicant should provide more elaborate characterization of the harvest characteristics using their device compared to standard of care. • Please provide a table with milliliters of aspirate, number of subset stem cell populations and other populations such as T cells compared to blood, the goals of the aspirate. • No, since it's not really clear what actual advantages are expected from these modifications. The data for the osteopenia cadaver are unconvincing. • The reduction of pain with this device is not clear.
GWG Votes	Is the proposal well planned and designed?
Yes: 3	*none*
No: 11	• The need for the modifications are unclear. • There are many unanswered questions about the efficacy and utility of this device. • Success metrics are not well defined. • No outcomes/success criteria are provided for any given stage. • There are concerns about vague outcome measures regarding how the iterations will affect the bottom line. If this device can help improve stem cell yield then shouldn't the stem cell target number be part of the outcome measures in the milestones? • There are concerns about the interaction of the flexible device and the sharp trocar. Can the rotating flexible aspirator be lacerated by the trocar? Can the coating be lacerated by the trocar? • There are concerns about the impact on osteopenic bone. How many cadaveric bones were studied? What was the tolerance of the material? At what point does this device penetrate cortical bone? It would be good to know the limitations of the device. • The risk of contamination needs to be evaluated.
GWG Votes	Is the proposal feasible?
Yes: 8	• The team assembled has strong collaborators. • Based on the previous work of the group the proposal is feasible.
No: 6	• Details and data in the proposal are lacking.
GWG Votes	Does the project serve the needs of underserved communities?
Yes: 8	• This product does not really have a special impact on the underserved because it would serve all populations equally.
No: 6	• Not particularly addressed. • Unclear.