TRANSLATIONAL AWARDS

$14,157,655 GWG RECOMMENDED

APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Resubmit.	Previous CIRM Funding	Disease Indication	Product Type	Approach
TRAN1-10958	Autologous iPSC-derived smooth muscle cell therapy for treatment of urinary incontinence	$5,977,155	**Y**	**90**	90	1	85	90	13	0	Y	Y	Urinary incontinence	Cell therapy	Autologous, iPSCs-derived progenitor smooth muscle cells
TRAN2-10990	Development of a Noninvasive Prenatal Test for Beta-Hemoglobinopathies for Earlier Stem Cell Therapeutic Interventions	$1,721,606	**Y**	**90**	89	2	85	90	14	0	Y	Y	Beta-hemoglobinopathies	Diagnostic	Non-invasive, Next Generation Sequencing of fetal DNA in maternal plasma
TRAN1-10937	Therapeutic development of an oxysterol with bone anabolic and anti-resorptive properties for intervention in osteoporosis	$1,689,855	**Y**	**85**	82	10	50	87	11	2	Y	N	Osteoporosis	Small molecule combination	Osteogenic compound combined with a bone-targeting and anti-resorptive agent
TRAN1-10995	Morphological and functional integration of stem cell derived retina organoid sheets into degenerating retina models	$4,769,039	**Y**	**85**	82	6	70	90	9	6	Y	Y	Retinitis pigmentosa	Cell therapy	Transplant of hESC-derived retinal progenitor sheets
TRAN1-11013	Stem cell gene therapy to restore blood flow in critical limb ischemia	$2,984,646	**N**	**80**	81	5	70	90	5	8	Y	Y			
TRAN1-11022	Targeted Activation of Bone Forming Stem Cells	$2,363,603	**N**	**80**	79	11	60	100	5	10	N	Y			
TRAN1-10941	A Neurogenic Neurotrophic Cytoprotective Compound (NNCC) for Acute Ischemic Stroke	$2,518,114	**N**	**80**	72	21	20	100	4	11	N	Y			
TRAN1-10954	Developing engineered autologous leukemia vaccines to target residual leukemic stem cells	$4,044,098	**N**	**75**	75	6	65	85	1	14	N	N			
TRAN1-11008	cGMP-grade placental stem cell production and characterization for treatment of congenital metabolic disorders	$5,707,518	**N**	**70**	66	10	45	75	0	15	Y	Y			
TRAN3-11060	Development of an osteoinductive device to treat osteoporotic vertebral compression fractures	$2,362,422	**N**	-	-	-	-	-	0	12	N	N			
TRAN1-11074	A novel small molecule for radiation bowel toxicity	$1,996,576	**N**	-	-	-	-	-	0	15	N	N			
TRAN1-10974	Treatment of glioblastoma (GBM) or other malignant gliomas (MGs) via overcoming c-Cbl inhibition and promoting oxidation-based activation of c-Cbl	$2,452,029	**N**	-	-	-	-	-	0	12	N	N			
TRAN1-11042	Stem cell derived neuronal cell transplantation to repair the phrenic network after cervical spinal cord injury	$2,057,487	**N**	-	-	-	-	-	0	15	N	N			
TRAN3-11055	Transvascular access and aspiration of thoracic duct lymph for progenitor cell harvest and infusion.	$1,886,238	**N**	-	-	-	-	-	0	14	N	N			

Application #	TRAN1-10958
Title (as written by the applicant)	Autologous iPSC-derived smooth muscle cell therapy for treatment of urinary incontinence
Translational Candidate (as written by the applicant)	Smooth muscle cell progenitors (pSMCs) differentiated from patient iPSCs which is injected into the urethral muscle to regenerate a weak urethra.
Area of Impact (as written by the applicant)	Surgery for urinary incontinence is effective in 80% of patients. Our target is those who failed surgery (20%), or those who cannot undergo surgery.
Mechanism of Action (as written by the applicant)	Our animal data suggest a paracrine stimulation of native elastin metabolism and smooth muscle cell engraftment with differentiation of these cells into terminal smooth muscle cells. Both effects are complimentary to urethral function; while elastin increases elasticity of the sphincter muscle, the regenerated smooth muscle cells provide the contractile forces required to close the urethral to prevent leakage of urine.
Unmet Medical Need (as written by the applicant)	Our target is those who failed surgery (20%) or those who are not candidates for standard therapy. This population is without options. This group is generally older and will increase drastically with the number of women with UI forecasted to increase by 55% by 20501 and as the US population ages.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Development of cGMP compliant procedures for isolation and production of patient iPSC lines • Development of cGMP compliant manufacturing process for iPSC-derived pSMCs and production of 3 pSMC pilot lots from patient iPSC lines • Perform preliminary toxicology, biodistribution, safety, potency, and efficacy studies using the pSMC pilot lots
Statement of Benefit to California (as written by the applicant)	Surgery for urinary incontinence (UI) is one of the most common indication for surgery in women with more than 210,000 women undergoing surgery for UI annually in the US. Unfortunately, 20% of these will fail. There is also a number of patients who cannot undergo surgery due to older age or medical conditions. This results in one third of older Californian women without options. This population will increase drastically with the number of women with UI forecasted to increase by 55% by 2050.
Funds Requested	$5,977,155
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

Scoring Data

Final Score: 90

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

Mean	90
Median	90
Standard Deviation	1
Highest	90
Lowest	85
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	0

Key Questions and Comments

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific 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	• There is a high potential for impact as there is an unmet need for alternatives to sling surgery. • The significance and impact are high because this is a patient population in need of new treatments. • Although surgical approaches to UI are effective they include mesh which some patients would prefer not to use, and about 20% of procedures fail. In addition, directly harvesting autologous muscle cells (smooth or skeletal) for urethral bulking is not feasible as these cells do not replicate in this patient age group. Lastly, a Phase III clinical trial for this indication has been terminated as there was no significant differences compared to placebo, leaving an unmet need for alternatives. • This product could provide a stem cell product, specifically progenitor smooth muscle cells, that would not only treat urinary incontinence but also other disorders such as rectal incontinence, gastroesophogeal disease, etc. • The proposed product would be excellent for poor surgical candidates and others who wish to avoid surgery. • Due to the increasing aging population, this is an important unmet medical need. It successful, it will improve quality of life and likely reduce costs.
No: 0	*none*

GWG Votes	Is the rationale sound?
Yes: 13	• Overall this approach is supported by our understanding of smooth muscle cell progenitors and their role in muscle biology. Each of the approaches to be utilized in this therapy have been applied in other endeavors. • This therapy should provide an improvement on both current treatments and other therapies currently or recently in clinical trials without requiring a huge leap of faith. • The project is sound as there have been a number of studies using muscle cells to treat UI. • The data presented in the proposal are compelling and support the development of the therapy. • A smooth muscle cell product from iPSCs is very logical and access to skin cells is relatively easy. • It is unclear whether there will be reliable generation of pSMCs for each patient and whether there will be sufficient sample size to determine patient to patient variability. The team presents data accrued from just 3 patients and plans to further test an additional 3 for pSMC generation in this proposal. • It will be interesting to see if "rejuvenation" of iPSC is a real phenomenon.
No: 0	*none*

GWG Votes	Is the proposal well planned and designed?
Yes: 13	• The investigators addressed concerns regarding teratoma formation and found that the incidence is negligible in cell doses less than 100,000. • The project plan outlined in the grant proposal will result in meaningful pre-submission meeting with the FDA. • The project plan outlined in the grant proposal is a well-constructed and will advance this therapy towards clinical development. • The reprogramming protocols from fibroblast to iPSC with mRNA/miRNA are well developed. • The GMP process development seems sufficiently robust.
No: 0	*none*

GWG Votes	Is the proposal feasible?
Yes: 13	• The proposed activities are on an ambitious schedule but doable by this expert team. The highly expert team is well able to adapt to necessary changes in studies (e.g. after a pre-

	pre-IND meeting with the FDA) despite the lack of a proper contingency plan in the proposal. • The proposed timeline is very aggressive and does not leave significant time for additional experimentation if required. • The investigative team is excellent. The concern is patient variability that may occur with transformation from iPSC to pSMC. • The staff appears well qualified to conduct the required activities. • It appears that the team will have access to all the necessary resources to conduct the proposed activities. • A specific risk mitigation plan has not been discussed in the proposal.
No: 0	*none*

Application #	TRAN2-10990
Title (as written by the applicant)	Development of a Noninvasive Prenatal Test (NIPT) for Beta-Hemoglobinopathies for Earlier Stem Cell Therapeutic Interventions
Translational Candidate (as written by the applicant)	An earlier, safer noninvasive prenatal screening test for β-thalassemia and sickle cell disease to identify candidates for prenatal stem cell therapy
Area of Impact (as written by the applicant)	Our test is safer and can be conducted earlier than the current methods of prenatal testing (e.g. chorionic villous sampling(CVS) and amniocentesis(amnio))
Mechanism of Action (as written by the applicant)	Our test uses next generation sequencing to analyze fetal DNA in a mother's blood in order to screen for β-thalassemia and sickle cell anemia. Counting sequence reads and comparing observed and expected values for the β-globin mutations allows the inference of fetal genotype. If the test is negative (fetus unaffected), the mother will be spared the invasive testing. If the test is positive (fetus affected), confirmatory testing can be pursued and stem cell therapeutic interventions considered.
Unmet Medical Need (as written by the applicant)	The availability of a safer and earlier fetal diagnosis, such as that afforded by our NIPT assay, will remove a critical bottleneck and greatly facilitate hematopoietic stem cell (HSC) transplants, currently the only curative therapy for the hemoglobinopathies.
Project Objective (as written by the applicant)	Assay ready for validation in CLIA-certified lab
Major Proposed Activities (as written by the applicant)	• Optimization of NIPT assay for autosomal recessive disorders and establishing cut-offs to develop an algorithm and software • Testing of performance characteristics to demonstrate analytical sensitivity, specificity, precision, and repeatability adequate for intended use • Demonstration of analytical accuracy on well characterized clinical samples and development of a clinical validation plan that meets CLIA requirements
Statement of Benefit to California (as written by the applicant)	California boasts one of the most ethnically diverse populations of the United States. The incidence of mutations causing diseases such as sickle cell disease, alpha-thalassemia, and beta-thalassemia, per 100,000 infants screened in California are 15.2, 11.1, and 1.8, respectively. As curative therapies involving stem cell transplants and gene editing become more readily available (after birth and intrauterine), earlier and safer fetal diagnosis will be critical for their implementations.
Funds Requested	$1,721,606
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

Scoring Data

Final Score: 90

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

Mean	89
Median	90
Standard Deviation	2
Highest	90
Lowest	85
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	14
(1-84): Not recommended for funding	0

Key Questions and Comments

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific 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	• There is a substantial unmet need and this approach constitutes a safe and effective way for earlier in utero diagnosis and management of beta-hemoglobinopathies. • The proposal represents a novel method for assessing autosomal recessive (AR) disorders early in pregnancy from fetal DNA. This proposal therefore has the potential to impact screening of other disorders beyond sickle cell anemia and thalassemia. • If the sensitivity and specificity is precise enough, this diagnostic will have significant impact. It has potential to be expanded to other indications as well. • This product would be very impactful for future intra-uterine stem cell transplantation. It would facilitate prenatal stem cell transplant for beta-hemoglobinopathies which has the potential to address an unmet need for a non-myleoablative, non-immunosuppressive cure for disease. • Even in absence of successful HSC transplantation, the product provides value to families with fetuses diagnosed with beta-hemoglobinopathies from a prenatal counseling perspective and in preparing for postnatal care. • A concern is that the bottleneck to successful HSC transplantation is not prenatal diagnosis and thus it is unclear if the product would accelerate the successful implementation of stem cell-based treatment.
No: 0	*none*
GWG Votes	**Is the rationale sound?**

Yes: 14	• The rationale for sequencing of fetal DNA isolated from maternal blood is sound and the potential for in utero transplantation is appropriate.
	• The rationale is sound; the mother's plasma will have DNA from the fetus.
	• There is potential impact on other autosomal recessive disorders.
	• The rationale and feasibility of the product is supported by previously published studies and the investigators own preliminary data.
	• Preliminary data demonstrates the technical feasibility of the product including:
	  ○ Ability to capture short fragments of DNA
	  ○ A capture probe that covers a large portion of the target beta-globin gene
	  ○ The feasibility of using linked SNPs to determine fetal genotype
	• If the target level of sensitivity is achieved, the test under development has the potential to reduce the number of higher-risk screening procedures (CVS and amnio) with minimal risk to patients, since only individuals that screen positive by the DNA test would require confirmatory testing by CVS or amnio.
	• The rationale that the current prenatal diagnostic modalities (CVS) are the limitation to implementation of HSC transplantation is a stretch.
	• The limited number of actual beta hemoglobinopathy patients that have been used in preliminary studies is a concern (although this is purpose of the proposal).

No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 14	• The applicants propose a well-constructed, methodological approach to ensuring accuracy and reproducibility of the product. • The proposal is well designed with clear points of go/no-go. • A methodological approach is proposed, with good assessment of success factors. • An appropriate timeline is presented with culmination of the plan to use the product in an established CLIA lab. • They have a significant amount of preliminary data to characterize the test, and the required additional characterization information needed can be obtained with minimal risk to patients.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**

Yes: 14	• The scientific and technical principles of the proposal are sound and based on state-of-the-art molecular sequencing methods. • Excellent team with available resources that allow for the design, optimization, and implementation of the product. • Collaborations already formed with a center that has a clinical trial for stem cell transplantation for alpha-thalassemia and pursuing one for sickle cell so they can hit the ground running. • Team is well positioned for success. • Excellent research team and timeline is appropriate. • The team is particularly strong. • The proposal identifies risks and mechanisms to overcome the risks. • Identification of risks and mechanisms to mitigate them are feasible.
No: 0	*none*

Application #	TRAN1-10937
Title (as written by the applicant)	Therapeutic development of an oxysterol with bone anabolic and anti-resorptive properties for intervention in osteoporosis
Translational Candidate (as written by the applicant)	A novel oxysterol with bone anabolic and anti-resorptive activity that will effectively and safely treat osteoporosis better than current options.
Area of Impact (as written by the applicant)	Osteoporosis that results in bone fractures.
Mechanism of Action (as written by the applicant)	The proposed candidate will target Mesenchymal Stem Cells in the skeleton to stimulate their differentiation into bone forming osteoblasts that will rebuild the bone lost to the disease. In addition, the candidate will exert anti-resorptive effects due to presence of the bisphosphonate Alendronate that inhibits bone resorption. The candidate is an orally administered treatment that is designed to be delivered to bone.
Unmet Medical Need (as written by the applicant)	The candidate fills a gap in bone anabolic agents for the treatment of osteoporosis. Currently only two FDA approved anabolic agents are available, both of which have limited use due to significant safety concerns and patient non-compliance due to daily subcu injections that cause adverse effects.
Project Objective (as written by the applicant)	Initiate IND enabling studies, and Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Scale up of candidate compound • Determination of optimum dosing and pharmacokinetics • Toxicology studies
Statement of Benefit to California (as written by the applicant)	Our program has the potential to have a significant positive impact on the lives of patients with osteoporosis, especially in California where its unique demographics make it particularly vulnerable. Latinos are 31% more likely to have osteoporosis than Caucasians, and California has the largest Latino population in the US, accounting for 39% of its population. Data suggests hip fracture incidence has increased among Latinos from 1983 to 2000, while it fell among non-Latino women.
Funds Requested	$1,689,855
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

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	82
Median	85
Standard Deviation	10
Highest	87
Lowest	50
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	11
(1-84): Not recommended for funding	2

Key Questions and Comments

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GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 13	• There is a substantial unmet medical need for treatment for osteoporosis. • Osteoporosis a significant health problem. • This product is designed to push differentiation of multi-potent mesenchymal stem cells towards osteoblasts in bone, as well as reduce bone reabsorption. This approach, if successful, could significantly improve patient care. • There is a huge unmet medical need as anabolic therapies are inconvenient and very expensive. • The potential of this product to safely promote anabolic growth would have significant impact.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• The rationale for combination therapy is sound, but data suggest that a combinatorial effect may not occur. • The pharmacological strategy for the product is well supported by our current understanding of bone biology and the available data. However, the translation of the rodent findings to humans may not be readily predictable. • The product has the potential to have a more rapid incremental increase in bone mass. • There is concern that the preclinical model will not predict the potential additive effects of anabolism and anti-resorption. • The clinical target has been validated.
No: 1	• More proof of concept data is needed before moving forward with larger animal models. Alternatively, a different bone loss model, a hind limb casting/immobilization model perhaps, would be beneficial. • It is unclear whether the compound is blunted by alendronate.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 11	• This is a well-constructed program that will meet the goal of conducting a successful pre-IND meeting with the FDA. • The proposed pre-IND development plan is complete and well designed. • The program should allow the investigator to make a data-driven decision on advancing the product into early clinical development. • The applicant was responsive to previous review feedback.
No: 2	• The applicant should seek guidance regarding which studies are most important for a pre-IND meeting as not all of the listed milestones are required for a successful pre-IND meeting. • The applicant should consider holding their pre-IND Meeting earlier in their timeline, though the overall development program for an IND is appropriate. • A large animal model to demonstrate an anabolic effect is preferred, as rat may not be the best animal model.
GWG Votes	**Is the proposal feasible?**
Yes: 13	• This is a well-constructed program that will meet the goal of conducting a successful pre-IND meeting with the FDA. • The proposed preclinical repeat dose studies will inform definitive pre-IND studies. • Further justification should be provided to support the need for the one month rodent study as most programs advance directly to GLP one month studies based on the proposed pilot study. • The timelines associated with the project are aggressive, but are obtainable. • The team is comprised of experienced drug developers with appropriate expertise. • This is a well-organized team, but stronger clinical input with a group of experts in clinical trials is recommended. • The proposal outlines a robust risk mitigation plan that discusses many of the common issues associated with small molecule drug development.
No: 0	*none*

Application #	TRAN1-10995
Title (as written by the applicant)	Morphological and functional integration of stem cell derived retina organoid sheets into degenerating retina models
Translational Candidate (as written by the applicant)	Retina organoid sheets (ROs) derived from CSC14 human embryonic stem cells (NIH registry line #0284) manufactured under GMP conditions
Area of Impact (as written by the applicant)	Retinitis Pigmentosa (RP) (irreversible loss of photoreceptors) due to mutation of photoreceptors and/or other retinal genes
Mechanism of Action (as written by the applicant)	Proposed mechanism of action is cell replacement, combined with trophic effects. Transplanted hESC-derived retina organoid sheets will mature into photoreceptors and integrate with the degenerate recipient's retina. Such transplants have improved visual acuity and responses to flashes of light in the midbrain (superior colliculus) of immunodeficient retinal degenerate rats (two different models).
Unmet Medical Need (as written by the applicant)	There is currently no treatment for retinitis pigmentosa which is designated an Orphan disease by the FDA. Therapies in current clinical trials only target trophic effects which are only effective in early stages to delay degeneration.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Establishment of Working Cell Bank, GMP implementation of retina organoid (RO) production, establish product specification and release criteria • Identify and demonstrate markers correlated with function after maturation in vitro; functional in vitro imaging (FLIM and HSpec) • In vivo pharmacology: demonstrate efficacy in immunodeficient and -competent rat model and in immunocompetent rabbit model of RP
Statement of Benefit to California (as written by the applicant)	Retinal diseases reduce the quality of life of patients, at significant cost to the health care system. The proposed replacement therapy is the only one that targets more mature disease stages of RP, for which no other therapy exists. An effective treatment will keep afflicted individuals productive, enhance State tax revenues and defray the healthcare cost burden to taxpayers. It will also lead to robust industry developments, effectively leading to job creation and tax benefits.
Funds Requested	$4,769,039
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

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	82
Median	85
Standard Deviation	6
Highest	90
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	9
(1-84): Not recommended for funding	6

Key Questions and Comments

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GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 15	• RP is a significant healthcare issue and the unmet medical need is clear. • RP is an unmet need and the extension to other diseases involving retinal degeneration may be possible, so the proposal could be significant. • Perhaps, but it is difficult to judge whether RO sheets will really have RP disease modifying activity. • The applicant provided a more focused patient population in this application.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• The available body of data including other labs using cell sheets support the product concept. • Cell sheets are a very reasonable platform, but the local (paracrine) effects are not particularly well-delineated in the proposal. • It is unclear whether RO sheets will really have RP disease modifying activity. • To some extent. Issues surrounding mixed cell transplants have not been addressed. The applicants say they have not seen problems and will look for migration of cells into other organs, but our concerns are migration and interference within the retina itself. These issues probably require experimentation at this stage rather than theoretical speculation. • The use of organoids could be better rationalized compared to use of purified photoreceptors.
No: 1	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 11	• The proposal is well planned and designed. • The proposal has good collaborators and clear contingency plan. • There is a clear timeline and developmental scheme. • The applicant provided additional data as well as reasonable justification for identified deficiencies from the previous review. • A practical concern is that the great majority of budget supports people, rather than technical projects that could be done.
No: 4	• For pilot study using humanized rat model, visual function testing should be performed in all animals to document no detrimental impact on normal vision/retina in these animals (caused by either the RO graft or by the potential inflammatory/graft rejection response). • It was unclear if an additional control of RO transplants in immune competent mice without immune suppression will be performed. • The applicant should consider giving immune suppressive drugs to immune-deficient animals to independently assess impact of those drugs on RO engraftment separate from immune rejection.
GWG Votes	**Is the proposal feasible?**
Yes: 13	• The team seems to have a coherent plan. • The plan and timeline are clearly designed with both sequential and parallel tasks and dependencies.
No: 2	• Many senior people are involved, and more salary is proposed than money for supplies. Technical staff are needed. • Budget seems too admin heavy.

Application #	TRAN1-11013
Title (as written by the applicant)	Stem cell gene therapy to restore blood flow in critical limb ischemia
Translational Candidate (as written by the applicant)	Human mesenchymal stem cells [MSC] transduced by a lentiviral vector to secrete supraphysiologic levels of vascular endothelial growth factor 165A.
Area of Impact (as written by the applicant)	Subjects with a clinical diagnosis of Critical Limb Ischemia, Rutherford category 4 or 5, who have failed traditional revascularization treatments.
Mechanism of Action (as written by the applicant)	MSCs are established angiogenic agents with a strong safety profile in clinical trials but have shown limited success in treating vascular disorders. VEGFs are ideal for promoting therapeutic angiogenesis, but sustained delivery in the damaged tissue has not been accomplished. We propose combining the stem cell and gene therapy approaches. Intramuscular injection of MSC/VEGF delivers local and sustained expression of VEGF to promote angiogenesis and local reperfusion of the ischemic tissue.
Unmet Medical Need (as written by the applicant)	Critical limb ischemia (CLI) represents a significant unmet medical need without any effective medical therapies for patients at high risk of amputation. Currently the only method of treatment for this very severe form of CLI is amputation. Costs and risks associated with limb amputation are high.
Project Objective (as written by the applicant)	Preparation for a Type C Meeting with the FDA
Major Proposed Activities (as written by the applicant)	• Develop, characterize, and evaluate cell banks of MSC/VEGF. • Confirm efficacy in rabbits and perform dose finding studies in clinically relevant mouse models. • Evaluate the distribution and persistence of cells and VEGF after treatment.
Statement of Benefit to California (as written by the applicant)	Critical limb ischemia represents a significant unmet medical need with no effective therapy for patients at high risk of amputation. Treatment results in a high economic burden to the healthcare system and the state. As a mechanism to treat this disease we engineered Mesenchymal Stem Cells (MSC), effective delivery vehicles for ischemic tissue, to produce high levels of Vascular Endothelial Growth Factor (MSC/VEGF), to enhance formation of new blood vessels. The goal is to prevent amputation.
Funds Requested	$2,984,646
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	5
Highest	90
Lowest	70
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	5
(1-84): Not recommended for funding	8

Key Questions and Comments

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

Yes: 13	• Critical limb ischemia is a public health imperative. The annual costs associated with lower extremity amputation exceed four billion dollars annually. Despite multiple trials, gene and cell-based approaches to limb preservation in CLI have not demonstrated efficacy. Patients with CLI who are not candidates for surgical or endovascular approaches to restoring limb perfusion represent an unmet medical need. • The product provides a new direction in gene and cell-based therapies that may have broad application to other diseases. • The product proposed in this application, MSCs transduced with a lentiviral vector to over express VEGF-A, represents the next generation in cell therapies. • The product may have a potential impact using transgenic MSC but provided data show does not indicate better outcome compared to wild-type stem cells. • Strong preclinical package overall. There may be some question as to the robustness of the VEGF-A pathway as a target; it seems logical but not proven.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 9	• The rationale is sound and is based on extensive in vitro and in vivo preclinical data that supports the proof of concept that is proposed. • The selection of VEGF-A as the target cytokine for over expression for limb ischemia is a concern as clinical trials using the plasmid or adenoviral vector (RAVE Trial) failed to demonstrate efficacy. • In response to a previous review, the investigative team has developed a large animal model of hind limb ischemia in the New Zealand White rabbit. By body weight, the NZW is 100 times larger than the mouse and 30 times smaller than humans, thus a relevant transitional model. • The team has been able to isolate and develop rabbit MSC/VEGF, jumping over several hurdles to do so, to provide an adequate control to compare to human MSC/VEGF in this immunocompetent model. This demonstrates the motivation and abilities of this team. • More evidence is needed that MSC-VEGF is better than MSC alone (or VEGF plasmid alone) in the rabbit model before investing in extensive master/working cell bank generation. • The project represents a step forward by evaluating genetically transduced MSC, which may provide advantages over using MSC + growth factors separately. However, initial data do not seem convincing.
No: 4	• It is unclear why VEGF-A was selected. The proposal appears to be based on results from 3 animals. • It is unclear whether the MSC/VEGF is really any better than the MSC alone. • The application would benefit from evidence that the MSCs expressing VEGF are actually better than MSCs alone. • Perhaps other angiogenic agents might be better than VEGF as well, or even a combination of agents would even work better. • Consider delaying development of the master cell banks until you have proof of concept evidence with the MSC/VEGF cells in the rabbit model. • There is already a plan to move forward with FDA but there are concerns with the possible outcome of the rabbit studies.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 7	• The team has manufactured and tested efficacy of a clinically compliant MSC/VEGF using a third-generation lentiviral vector, without other transgenes, thus diminishing immunogenicity of the vector, with a limit of 1-2 pro-viral insertions per cell, thus decreasing the risk of insertional mutagenesis. • The data contained in the proposal as well as the associated references provide compelling results that MSCs transduced to overexpress VEGF promote limb perfusion. However, data comparing MSC/VEGF does not reveal a difference to MSC, only normosol. • The data presented is not convincing that MSC/VEGF compared to natural MSCs is superior in promoting perfusion in ischemic limbs through angiogenesis. • Comparison of MSC/VEGF to plasmid VEGF and adenoviral VEGF in the NSG hind limb model is critical to demonstrate the cell-based delivery is more effective than the previous methods that have failed in clinical trials. • More information on the rabbit animal model and the potential need for immune suppression when using human cells is needed.

	• The investigative team has developed GMP compliant procedure to isolate and expand MSCs from adult human bone marrow.
No: 6	• The rabbit model is outstanding, especially the ameriod constrictor model. However, efficacy in the rabbit model of how MSC/VEGF is better than MSC alone is needed prior to any other manufacturing: a go/no go type of decision. • There are concerns regarding success in the rabbit model; this should be performed first and then move to other studies if it is successful. • Additional dosing data and multiple dosing is needed and is likely to be important given the short residency of the cells in vivo. • The team lacks clinical trial design expertise. • The team may have to rethink the MSC generation process and animal models using more samples. • There is a need for justification of multiple master cell banks and working cell banks.
GWG Votes	**Is the proposal feasible?**
Yes: 13	• The transgenic MSC directed therapy is feasible but may not have the expected results. • It is unclear why the cells are not being manufactured using bioreactors and why it is necessary to generate master cell banks at this stage as opposed to using non-master cell bank cells. • The cell production team is capable and have developed a GMP facility for their cell production, however there is a lack of experience in clinical trial design. The vascular surgeon who will provide guidance in trial design and execution lacks any experience in translational research and designing or running a clinical trial. • The pre-IND plan provides a clear roadmap. • The well-experienced team is a strength.
No: 0	*none*

Application #	TRAN1-11022
Title (as written by the applicant)	Targeted Activation of Bone Forming Stem Cells
Translational Candidate (as written by the applicant)	A combination product for bone regeneration.
Area of Impact (as written by the applicant)	Severe bone fractures that fail to heal and often require repeated surgeries or amputation.
Mechanism of Action (as written by the applicant)	This product utilizes ultrasound to deliver a bone-forming gene to stem cells that are recruited to the fracture site from the patient's own reservoir. As we have already shown, the gene triggers the cells to regenerate the bone that had been damaged, without the need for additional implants or surgeries.
Unmet Medical Need (as written by the applicant)	There are 11-15 million fractures per year and up to 12% do not heal properly. Current treatments that include bone graft implantation have multiple disadvantages like prolonged pain, high failure rate, risks of additional surgeries and more. There is an unmet need for new and effective solutions
Project Objective (as written by the applicant)	Type C meeting with the FDA
Major Proposed Activities (as written by the applicant)	• A large animal study to demonstrate the potential of the product to repair larger bone defects. • Obtain FDA feedback on the suitability of animal studies for an IND application.
Statement of Benefit to California (as written by the applicant)	Massive bone fractures are a complex medical problem that often requires bone grafting. We propose to develop a novel approach for the treatment of such fractures, which involves the delivery of a bone-forming gene to stem cells, resulting in bone regeneration. Such a treatment will benefit the citizens of California by reducing loss of workdays, duration of hospital stays, operative costs, and by improving quality of life for Californians with complex bone fractures.
Funds Requested	$2,363,603
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	79
Median	80
Standard Deviation	11
Highest	100
Lowest	60
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	5
(1-84): Not recommended for funding	10

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 scientific 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	• Large defects in bone fractures is an unmet medical need. • Ultrasound is known to deliver a gene to the site of interest and this technology can be applied to deliver BMP to the site of MSC-laden scaffold at the site of fracture. • There is some concern that the time line should be accelerated to be more competitive with current activity in the field.
No: 2	• The benefits may be a bit overstated as they state, "full rehabilitation can take an additional 12–52 weeks", but typically these longer impairments/rehab involved joint issues rather than just bone repair. • The FDA cautions that no clinical study has been able to demonstrate a decrease in healing time in bone fractures and suggests the applicants carefully determine what would be positive outcomes. • It appears that the product seems to improve healing in certain types of well-controlled breaks, but it is unclear if it is better than the current standard, even including removing the need to harvest bone from other areas. • Other methods to address this need are very far along and so the 30-month timeline might come in too late to be commercially viable. • It is difficult to assess the product as compared with use of individual components that go into the proposed combination therapy.
GWG Votes	**Is the rationale sound?**
Yes: 14	• The rationale makes sense and appears to work in preclinical models. They have been responsive to the FDA concerns and are moving into a second animal model for testing. • The combination therapy approach and use of ultrasound delivery may be better than the current standard. • Solid preclinical in vivo package with small and intermediate size animal models. • Novel use of improving incorporation of osteoblastic agent into the scaffold. • Addressed FDA's concern regarding animal model.
No: 1	• The combination of three different technologies make the proposal challenging with respect to FDA approval.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 5	• The large animal model is consistent w/FDA feedback. • The timeline of completion in a competitive marketplace is a disadvantage.
No: 10	• In the lab setting with very well controlled breaks, the scaffold will be placed similarly, but in real world breaks, the scaffold component will be folded and packed into the defect in different ways. The amount of folding and packing is likely to alter the effective porosity, among other properties, thereby impacting the ability of cells to migrate in to this component. This should be tested or standardized in the preclinical study in order to maintain consistency between subjects. • The effect of high intensity vs low intensity pulsed ultrasound on the bone healing should be discussed. • Controlling acoustic pressure seems to be critical for effective operation of the product. There seems to be a sweet spot, as too little or too much is significantly less effective. They did do some phantom studies but these are challenging and distance from the ultrasound probe to treatment site will vary along with the quality of the intervening tissue. Additional testing to find the ranges of acoustic pressure should be performed. • An ultrasound only group in the large animal model is needed, as there is some indication ultrasound may have some effects alone. • Better assessment of individual components as compared with combination therapy is needed. • There are potential problems with controls for the ultrasound and potential lack of experience on the team with the large animal model. • There are concerns about the appropriate clinical team. • Expertise in fracture healing/surgery in large animal models is needed. • There is no orthopedic surgeon as part of the research team to provide expertise in fracture physiology. • The timeline should be condensed.
GWG Votes	**Is the proposal feasible?**
Yes: 13	• All the components are in hand. However, there is major competition in this space and the 30-month timeline is problematic because of this competition.

	• This is a good group of researchers with good facilities, but an orthopedic surgeon should be added. • Many potential competitors that may be further ahead. A shorter timeline would be advantageous.
No: 2	• The timeline is questionable. • An orthopedic/trauma expert is needed.

Application #	TRAN1-10954
Title (as written by the applicant)	Developing engineered autologous leukemia vaccines to target residual leukemic stem cells
Translational Candidate (as written by the applicant)	Universally applicable, patient-specific leukemia vaccine, engineered to express a novel immune stimulatory combination for post-remission therapy
Area of Impact (as written by the applicant)	There is a critical and unmet need for new and safe treatment for older acute myelogenous leukemia (AML) patients whose current prognosis is poor
Mechanism of Action (as written by the applicant)	In older patients with AML, treatment with chemotherapy can produce remission in about half of patients. However, the vast majority of these individuals relapse within a year due to the persistence of residual leukemia cells. This engineered vaccine is designed to stimulate the patient's own immune system to generate leukemia-specific immune cells that can recognize, and kill residual leukemia-initiating cells. Vaccination after remission induction could increase relapse-free survival.
Unmet Medical Need (as written by the applicant)	For transplant ineligible older AML patients, outcomes are dismal and effective immunotherapies are needed. We have shown that by treating with AML cell vaccines, engineered to more effectively stimulate anti-leukemic immunity, we can eradicate established leukemia in pre-clinical models.
Project Objective (as written by the applicant)	Submit pre-IND package/conduct pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Produce viral vector using clinical production methods and finalize steps for using virus to engineer novel patient-derived AML cell vaccines • Finalize methods to collect, freeze, and engineer patient AML cell vaccines; Evaluate specificity of immune responses to AML versus normal bone marrow • Generate engineered AML vaccines in a cell therapy production facility to establish and validate clinical manufacture; Prepare for pre-IND meeting
Statement of Benefit to California (as written by the applicant)	Curative AML treatment requires referral to a major medical center and toxic inpatient therapy, creating financial and geographic challenges. However, most patients relapse. Our AML vaccine is a powerful strategy for converting patients' leukemia cells into effective vaccines that stimulate anti-leukemic immunity. Out-patient treatment with AML vaccines could be effective, less toxic, and more accessible to AML patients.
Funds Requested	$4,044,098
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 75

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	75
Median	75
Standard Deviation	6
Highest	85
Lowest	65
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	1
(1-84): Not recommended for funding	14

Key Questions and Comments

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific 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	• AML has limited therapeutic options and is an important disease to study. • The development of immune strategies outside of allogeneic bone marrow transplantation for AML would be useful. • This has excellent potential for impact in AML treatment, and the concept for an intradermal vaccine is promising and exciting.
No: 3	• The unmet medical need is there but it is not clear that the experimental plan will have impact as described: It is not clear that they will be able to target stem cells and not clear that in the post-treatment period there will be vaccine response.
GWG Votes	**Is the rationale sound?**
Yes: 5	• Mostly yes, but it is unclear how to ensure that the intervention will have a AML stem cell effect. • The experiments in the leukemia mouse model are compelling, though limited. • The application could be improved with additional data that more clearly suggests the vaccine has a good chance of working as proposed.
No: 10	• More POC data is needed to determine if this is ready to move forward. • There is no clear evidence that the leukemic stem cells would be effectively targeted by this approach. • There is no clear rationale for why the vaccine would target leukemia stem cells. • There is no plan to isolate AML stem cells for the vaccine, the vaccine will be with bulk cells. • There is no data provided to support that patient T cells will be able to respond to the vaccine in the post-treatment period. • It is not clear that any immune reactivity that is meaningful (i.e., actually targets and kills AML) can be generated in the post-induction phase of treatment. • The evidence provided using allogeneic T cells is not relevant, as the effect must be mediated by patient T cells which are likely to be less effective. • The therapy would be used very early in course of disease as opposed to more realistic later stages with higher tumor burden.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 8	• The milestones are well designed for the length of the award, and likely to lead to an informative pre-IND meeting. • The proposal is reasonable as far as generating useful pre-IND data. • The most robust studies would involve treatment of mice with actively growing AML (PDX) as well as autologous T cells which are then vaccinated and the remaining AML transplanted into secondary recipients. • Mostly yes, but it is unclear whether high-dose chemotherapy will attenuate the immune response. • While the PDX experiments are not likely an absolute requirement for the FDA, they are an important part of the development program that will answer many questions about how this vaccine may impact AML cells and possibly leukemia initiating cells.
No: 7	• The applicants need to show that the vaccine is effective by in vivo treatment.
GWG Votes	**Is the proposal feasible?**
Yes: 13	• The proposal is feasible given the expertise of the team. • The current proposed timeline is well thought out and appears feasible. • Overall, the project has an excellent chance for success, though there is significant risk in gaining meaningful information from the PDX experiments. • The team is top-notch.
No: 2	• The in vivo efficacy of the vaccine is questionable.

Application #	TRAN1-10941
Title (as written by the applicant)	A Neurogenic Neurotrophic Cytoprotective Compound (NNCC) for Acute Ischemic Stroke
Translational Candidate (as written by the applicant)	Neurogenic Neurotrophic Cytoprotective Compound (NNCC)
Area of Impact (as written by the applicant)	Stroke is treated with reperfusion therapy, but most patients do not fully recover. New or adjuvant therapies are required to promote full recovery.
Mechanism of Action (as written by the applicant)	The efficacy of this product is related to cytoprotection against a wide variety of insults present during the initial ischemic event, neurotrophism related to neurotrophins (i.e.: BDNF), and they may offer the possibility of promoting regenerative process induced by growth factors or the recruitment of endogenous precursor stem cells. This is a unique compound, and an exceptional opportunity to treat stroke by providing neuroprotection, neurotrophism and stem-cell mediated tissue repair.
Unmet Medical Need (as written by the applicant)	In CA, stroke is treated with tissue plasminogen activator (rtPA) and thrombectomy reperfusion, but the majority of patients do not fully recover. We propose to use a novel small molecule that produces cytoprotection and also enhanced neurogenesis to treat victims to maximize clinical recovery and reduce societal burden.
Project Objective (as written by the applicant)	Pre-IND and subsequent clinical trial initiation.
Major Proposed Activities (as written by the applicant)	• IV formulation and PK in 2 species • Efficacy and safety testing in rodents of age with mixed gender, rabbits of mixed gender, and non-human primates • pre-IND preparation
Statement of Benefit to California (as written by the applicant)	The ability to prevent neuron cell death and stimulate the production of new neurons, which already takes place to some limited extent in the stroked brain, through the use and advancement of NNCC'S to treat acute ischemic stroke, could have a tremendous impact on a large patient population in California and worldwide. This program offers a realistic multimodal adjuvant therapeutic option to stroke victims. We will advance this product to treat Acute Ischemic Stroke to an IND.
Funds Requested	$2,518,114
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	72
Median	80
Standard Deviation	21
Highest	100
Lowest	20
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	4
(1-84): Not recommended for funding	11

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 scientific 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	• Acute stroke management is a large unmet medical need. • This product is a neuroprotective compound that can be useful if administered early. • This is a very translational project that will impact the treatment of stroke patients. • There are major unmet needs in stroke as there is a tight time window for rtPA use. • New and novel treatments are needed. • It is unclear whether this compound really has a stem-cell modifying activity.
No: 2	• Data in a stroke model is needed to demonstrate benefit. • The data are not convincing regarding neurogenesis.
GWG Votes	**Is the rationale sound?**
Yes: 10	• Well-rationalized project. • There are questions if the product is actually neurogenic, and the team more or less answers the question, but likely the true answer is hard to get at and may not be needed at this point if the treatment works. • Most data is from Alzheimer's disease models. This proposal addresses this in multiple stroke animal models.
No: 5	• Stronger proof of concept data and demonstration of a neurogenesis effect is needed. • The neurogenesis component not well supported. • A rationale for the sample size calculation is needed. • A rationale for the dose calculation is needed. • There is good data with neuroprotection but insufficient data for neurogenesis. • The proposed preclinical in vivo models seem disjointed in that key endpoints are not consistent.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 7	• The study is well-planned and designed. • The project needs better project management, given its size and complexity. • The large animal work is an outstanding effort, but may be more than needed at this stage. However, the imaging will be additive. • The timing of dose is addressed in some ways, and likely good starting points. • It is unclear if repeat doses will be needed.
No: 8	• Sufficient rationale is not provided for timing of dosing, discussions on number of dose levels, or rationale for dose levels. • The time frame for measures is not well described. • It is unclear how the experiments in the different species build on each other.
GWG Votes	**Is the proposal feasible?**
Yes: 12	• Excellent team and resources. • Very feasible grant. • Greater clarity in critical success factor(s) of the preclinical in vivo models is needed.
No: 3	• A program manager may be needed. • A financial contingency plan is missing. • Clear go/no go decisions are a strength.

Application #	TRAN1-11008
Title (as written by the applicant)	cGMP-grade placental stem cell production and characterization for treatment of congenital metabolic disorders
Translational Candidate (as written by the applicant)	We will produce therapeutic grade placental stem cells that possess hepatic differentiation capability and contain abundant lysosomes.
Area of Impact (as written by the applicant)	Cell replacement therapy for congenital metabolic disorders will be possible with the non-tumorigenic and readily available placental stem cells.
Mechanism of Action (as written by the applicant)	Upon liver-directed cell transplantation, the engrafted placental stem cells (hAECs) will differentiate into hepatic cells and provide hepatic and lysosomal metabolic enzyme functions. By compensating for the patient's missing enzyme function, the disease symptoms will be improved.
Unmet Medical Need (as written by the applicant)	Currently, there are no definitive therapies for congenital metabolic disorders. These disorders can be treated by hAEC transplantation.
Project Objective (as written by the applicant)	Obtain data for successful pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Isolate hAECs with a clinically applicable protocol under cGMP conditions • Evaluate the quality and therapeutic potential of isolated cells • Catalog the therapeutic grade hAECs with the HLA type and cryopreserve them to produce a Bio-Bank
Statement of Benefit to California (as written by the applicant)	If successful, the proposed project will lead to initiating a novel stem cell therapy for congenital metabolic disorders in California. Therefore, the potential benefits will be 1) providing the new therapy to the Californian patients with unmet medical needs, 2) increasing visiting patients from outside of the State for the treatment, and 3) creation of new cell therapy related medical industry jobs for Californians.
Funds Requested	$5,707,518
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	66
Median	70
Standard Deviation	10
Highest	75
Lowest	45
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 scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 13	• The congenital metabolic disorder, an ultra-rare disease, is an unmet medical need. • The use of non-immunogenic stem cells to treat the congenital metabolic disorder by making functional hepatocytes could be impactful. • This is a novel approach to a potentially difficult long-term problem. • Interesting cell type with potentially important properties.

	• Overall, the applicants did a good job of addressing the previous critiques. Experts were added to guide them through the process to an IND. • In the resubmission, they have reduced the testing to one indication which is a plus, as the technology could impact multiple other indications as well.
No: 2	• Important area of unmet medical need but the research plan is not likely to be impactful.
GWG Votes	**Is the rationale sound?**
Yes: 8	• This is a rational approach for enzyme replacement. • This appears to be better than enzyme replacement or transplantation of hepatocytes, including some immunologic advantage in using these cells. • The selection of CD45 negative cells from the placenta is rational because these cells will be less immunogenic, but transdifferentiation and long-term survival after intrasplenic injection is questionable. • This proposal will test the cells in adult mice to determine if the cells will engraft in the same way as mice with immature livers as has been tested previously. This is new to this revision and vitality important. • More proof-of-concept experiments are needed before any cell banking activities take place. • Generally good response to previous comments.
No: 7	• There are concerns regarding immunogenicity and discussion of HLA, route of administration, and biobanking. • There is insufficient data to demonstrate efficacy.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 1	*none*
No: 14	• More proof-of-concept experiments demonstrating the therapy works in adult mice are needed prior to any cell manufacturing or banking activities. • Preclinical in vivo proof-of-concept is needed. Route of administration, administered dose range, and durability of response are not fully understood. • Dosing (amount, timing and frequency) is unknown at this point but will be tested (amount and timing) in this proposal. • It is unclear how the number of cells to be administered will be determined. • The FDA had proposed that a POC study be completed in order to submit a pre-pre-IND. It is important to understand dose response. • The route of administration needs to be clarified. • The cells will be injected into mouse spleens in the preclinical studies, but the applicants propose direct portal vein injection into patients. A slow release vs bolus may affect cell engraftment. • It is unclear whether multiple injections be needed. • Durability of the treatment appears unknown and is only partly addressed in the revised proposal (3-month follow-up). A longer follow-up is suggested. • The design of a tumorigenicity study is premature - this study should not be initiated without concurrence of study design by the FDA. • It is unclear if the immunologic advantages are still present when the cells mature in vivo. • HLA type distribution should be done first, followed by selection of donors to make the bank. • A better understanding of immunogenicity and HLA matching requirements is needed. • A better understanding of the demands of biobanking particularly with regard to HLA matching a population is needed. • The GMP facility and collection process are not stated.
GWG Votes	**Is the proposal feasible?**
Yes: 8	• Feasible but need clear GMP-grade facility and collection process. • Good fundamental aspects but the team needs to develop a more coherent plan. • HLA matching is a significant issue that needs to be worked out, but treatment with immunosuppression is probably OK. • There is little discussion of risks, including the longevity of the engrafted cells and if the cells don't work in adult mice. • The trial in Europe would provide insights that influence this study, thus a reason to wait for at least some of those results before starting this study.

No: 7	• More proof-of-concept experiments are needed before any cell banking activities take place. • HLA banking appears to be unfeasible. • There is insufficient time and staff for manufacturing activities. • More clinical input is needed, someone experienced with the congenital metabolic disease.

Application #	TRAN3-11060
Title (as written by the applicant)	Development of an osteoinductive device to treat osteoporotic vertebral compression fractures
Translational Candidate (as written by the applicant)	A drug-device combination product, as an osteoinductive device to treat osteoporotic vertebral compression fractures (OVCFs)
Area of Impact (as written by the applicant)	Osteoporotic vertebral compression fractures
Mechanism of Action (as written by the applicant)	This is a unique product that works by delivering naloxone (the small molecule component) during a surgical procedure in conjunction with a simple collagen-based carrier, and recruits endogenous mesenchymal stem cells (MSCs). In osteoporotic vertebral compression fracture patients with a significant vertebral fracture, this product can be placed into the vertebral body with passive grafting material to speed osteo-integration.
Unmet Medical Need (as written by the applicant)	Osteoporotic vertebral compression fractures (OVCFs) are increasingly common, especially among the elderly (550,000 to 700,000 patients annually). Available treatment options for OVCFs are mostly palliative and not efficient, underscoring a significant unmet medical need.
Project Objective (as written by the applicant)	Pre-IDE meeting with FDA
Major Proposed Activities (as written by the applicant)	• Optimize the compositional attributes of the bone graft implant • Validate the final embodiment of the product using (a) rat glucocorticoid induced osteoporosis and (b) rabbit posterior lumbar spine fusion models • Prepare for commercial grade manufacturing of the product, and conduct a pre-Investigational Device Exemption (IDE) meeting with the FDA
Statement of Benefit to California (as written by the applicant)	Our study will lead to the development of a new bone grafting material and the production of a novel, commercial grade product that strongly stimulates bone growth and is ready for clinical investigation. Successful development of the product will also directly benefit the State of California and its citizens by significantly reducing the number of hospitalization days, overall cost on healthcare system, productivity, and increase the quality of life for osteoporosis patients at high risk of OVCFs.
Funds Requested	$2,362,422
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	12
(85-100): Exceptional merit and warrants funding, if funds are available	0
(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 scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 4	• The proposed product addresses a medical need for which there are currently available therapies, as summarized in the proposal. However, the proposed product may provide an improvement in the efficacy of therapy, as compared to current standard of care. • The device covers an unmet need, but it is unclear if the product is better than current methods. • The approach is novel but insufficient pre-clinical evidence of potential efficacy.
No: 8	• There is an unmet need for new treatments for painful vertebral fractures. • The public health need is still substantive, but the proposed efficacy hurdle is too low, namely comparability in terms of "pain" and "function" @ 6 months.
GWG Votes	**Is the rationale sound?**
Yes: 4	• It is logical to approach this problem in this manner. The existing data base is limited, though, and the opioid receptor pathway is not well-accepted as a robust one. • Potentially interesting pathway and mechanism of action.
No: 8	• In vivo data is promising but limited. • The small amount of data is incompletely described. • The animal models are not convincing, poorly described, and have a small 'n' value.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 2	*none*
No: 10	• More preclinical mechanism of action studies are needed. • There is a lack of quality assurance expertise on the team. • As a medical device, the team will need to instigate a quality system in compliance with 21 CFR 820. At a minimum, evidence of design control will need to be available for the IDE. This should be considered now, rather than retrospectively. • The proposal does not realistically anticipate regulatory issues. • The project plan is well designed, but timelines are very ambitious and will most probably slip, despite the experience of the assembled team.
GWG Votes	**Is the proposal feasible?**
Yes: 3	• The project plan is feasible and the team is experienced. • Consider earlier interaction with FDA concerning the pre-clinical testing plan and need for human clinical testing. • Good plans for dealing with regulatory process.
No: 9	• Timelines do not reflect an understanding of the work required. • Timeline is too aggressive for the complexity of device, collagen, and novel osteoblastic pathway. • The risks outlined are very generic.

Application #	TRAN1-11074
Title (as written by the applicant)	A novel small molecule for radiation bowel toxicity
Translational Candidate (as written by the applicant)	A novel small molecule that preserves stem cells but not tumor cells.
Area of Impact (as written by the applicant)	Clinical oncology/Radiation treatment for cancer.
Mechanism of Action (as written by the applicant)	In the case of clinical treatment with radiation and chemotherapy, normal tissue damage happens both long term and short term to patients both affecting the ability to proceed with therapy or not and the quality of life for the patient. At the heart of the tissue response is resident stem cells. This product acts by preserving stem cells within the gastrointestinal tract/ epithelium to allow normal tissue regeneration while not protecting tumor tissue. This facilitates a greater therapeutic index.
Unmet Medical Need (as written by the applicant)	There are no drugs which can ameliorate small bowel toxicity or epithelial toxicity to radiation and/or chemotherapy. Further, the number of patients suffering from bowel dysfunction from this damage exceeds the number diagnosed with Crohn's disease. It is a neglected area.
Project Objective (as written by the applicant)	Pre-IND readiness and meeting scheduled.
Major Proposed Activities (as written by the applicant)	• Demonstrate oral availability and characterize dose response. • Safety profile created. • Key rodent studies introducing chemotherapy vs. just radiation to understand the product with the major elements of standard of care.
Statement of Benefit to California (as written by the applicant)	We are a California company. California is a leader in the Stem Cell area in the United States and our vision is to build a company with a portfolio of drugs targeting the stem cell regenerative medicine space. We feel this is a new area which can create jobs, change how medicine is conducted and increase the effectiveness of conventional therapies starting here in California.
Funds Requested	$1,996,576
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 scientific 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 product would offer a sufficient, impactful, and practical value proposition for patients as it would alleviate the off-target effects associated with radiation or chemotherapy, resulting in fewer side-effects for patients. If successful, this product could allow for more aggressive anti-tumor treatment regimens. • The proposed strategy may be useful in alleviating GI toxicity. • The product would offer a sufficient, impactful, and practical value proposition for patients and may allow more aggressive treatment, with fewer side effects. • Very exciting science that could have a significant impact on oncology.
No: 7	• Mitigating the high dose radiation effects on the intestinal toxicity is significant but the proposed small molecular agent may not work as the applicants hypothesize. • Important area of medical need but proposal and plan are not likely to have impact. • Strengths are much of the preliminary work has been published in peer-reviewed journals. • The authors specifically wish to focus on bowel toxicity following radiotherapy – but it is unclear throughout their proposal whether they are specifically focusing on the small intestine, large intestine or both. This is a significant concern with this project, as many of the side effects following radiotherapy affect the large intestine, with particular emphasis on bleeding, diarrhea and constipation. • The investigators need to do further work on positioning the drug. They must be able to show their drug improves the clinical symptoms of radiation (i.e. patient care with reduced diarrhea; reduced bleeding; improved constipation; improved weight loss). Patients simply won't care if they have increased intestinal stem cells if their clinical toxicities following radiation do not improve.
GWG Votes	**Is the rationale sound?**
Yes: 3	• In general, the approach is based on sound scientific rationale. The approach is based on the role that stem cells have in epithelial cell regeneration following tissue injury from radiation or chemotherapy. However, mechanism by which the product preserves stem cells has not been elucidated at this point.
No: 12	• The literature that this application has cited suggests the authors do not have a detailed understanding of the underlying mechanisms of toxicity and indeed fail to cite the seminal papers in this field. Specifically, the authors state that epithelial toxicity is a result of chemotherapy/radiotherapy directly damaging epithelial cells lining the GI tract – which leaves the tissue open to infection and ulceration. This rather simplistic statement fails to take into account the plethora of literature which indicates it is much more complex than this; including involvement of bacteria; tight junctions; immune cells; submucosa cells amongst others. • The authors state they have screened over 70 cancer models, most of which were in vitro. However, in the publication cited, no evidence of the animal tumor models referred to could be identified. • The proposal is very confusing, it is unclear how and why this should work. • The investigators state that stem cells are key players in the response and outcome of patients. Despite this statement, they have not presented any clinical data to support this. All of the data that has been presented within this study is pre-clinical or organoid. • It is unclear why this product would specifically target the epithelial stem cells. A possible mechanism of action is not described. • There was an apparent lack of understanding of WNT pathways. • The WNT pathway is attractive in the broader sense. However, there is concern on the lack of data on specificity of the WNT pathway (LRP specificity, Frizzled, and WNT ligand subtype) • There is concern that the product may protect residual cancer cells as well. • Targeting only stem cells will not decrease the toxicity/diarrhea due to loss of endothelial cells, loss of tight junctions and infection. • It is unclear how impacting the stem cells would translate to improvement of clinical symptoms. • Based on published data the rationale is sound.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 1	*none*
No: 14	• Overall whilst the project is feasible, there is concern the project will not answer the questions and hypothesis proposed.

	• In general, the program needs significant modification to meet the goal of conducting a meaningful pre-IND meeting with the FDA. Several of the go/no go criteria should be revised as the product will be used in combination with radiation and chemotherapy, therapies known to have associated toxicities including genotoxicity. • The study design is not clear. • The experimental plan is confusing, with no rationale supplied for the selection of species and doses for animal experiments. • There is no clear rationale for switching the animal model. • Unclear rational for specific (e.g., dosing) methodology. Studies examining the tumor promoting potential of the molecule should be included. • A tumor should be implanted into the animal model to determine if the compound also does not protect the tumor in vivo as well as in vitro. • The investigators need to demonstrate/explain how the specificity of protection is restricted to normal cells. • A comparison between the product and other approved drugs would be important for determining whether the product mitigates radiation effects.
GWG Votes	**Is the proposal feasible?**
Yes: 6	• The product has potential. The data presented are valuable but we have an insufficient foundation to advance this product. There is no evidence presented within the application which suggested this drug will improve patient outcomes. This information is not presented in preclinical models which makes it difficult to extrapolate whether this would also occur in humans.
No: 9	• As written, the proposal is confusing and the feasibility of completing the proposed studies within the timeline is questionable. • In general the staff seem qualified to conduct the required activities; however, it is recommended that the grant submitters consult with a toxicologist with small molecule experience on the design and conduct of rodent and non-rodent safety assessment studies.

Application #	TRAN1-10974
Title (as written by the applicant)	Treatment of glioblastoma (GBM) or other malignant gliomas (MGs) via overcoming c-Cbl inhibition and promoting oxidation-based activation of c-Cbl
Translational Candidate (as written by the applicant)	Maprotiline [FDA-approved antidepressant] in combination with Tamoxifen eradicates GBM cancer stem cells and stops GBM growth in animal models.
Area of Impact (as written by the applicant)	Glioblastoma is one of the most lethal cancers, with a medium survival of 12-18 months and no effective treatment to significantly increase survival.
Mechanism of Action (as written by the applicant)	Our therapy harnesses the c-Cbl tumor suppressor protein. C-Cbl modulates degradation of proteins critical in cancer stem cell (CSC) survival. GBM growth, and cancer stem cell (CSC) maintenance, requires c-Cbl inhibition via a complex with Cool-1/ßpix protein. The proposal is based on two critical discoveries: we identified an existing drug (Maprotiline) with the novel function of restoring c-Cbl function; and, found a candidate biomarker to enable screening of GBM patients most likely to benefit from therapy.
Unmet Medical Need (as written by the applicant)	GMB is the most common and aggressive brain cancer. Despite surgery, radiation and chemotherapy (temozolomide followed by bevacizumab at recurrence), the median survival has improved only to 18 months in the last decade. Once GBM recur they are universally fatal with no other treatments available.
Project Objective (as written by the applicant)	Pre-IND meeting for a Phase 2 GBM efficacy trial
Major Proposed Activities (as written by the applicant)	• Examine the relevance of c-Cbl function to treatment of other high-grade gliomas through analyses of tumor specimens and patient-derived cell lines • Test if c-Cbl-based treatments increase sensitivity of GBMs and high-grade gliomas to irradiation and other therapeutically relevant interventions. • Test if the presence of C1ßp phosphorylation enables the prospective identification of patients most likely to benefit from the c-Cbl based therapies
Statement of Benefit to California (as written by the applicant)	With limited funding for medical research and health care, it is in the best interest of the State to invest in projects that are immediately and directly clinically applicable. Given the poor prognosis and the high financial burden associated with GBM there is a strong sense of urgency to develop more effective, reasonably priced treatments. This is especially important given the growing number of patients affected by GBM in the US, 12% of which are represented by the citizens of California.
Funds Requested	$2,452,029
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	12
(85-100): Exceptional merit and warrants funding, if funds are available	0
(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 scientific members of the GWG were asked to

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 6	• GBM is an enormous unmet need. The described treatment and new biomarkers of response could have impact. • There is a huge unmet need, but since they already have an IND for this indication, there doesn't appear to be a need to conduct these experiments.
No: 6	• The proposal is an extension of studies done at another institution and may not be impactful. • Advancing this therapy forward in clinical development can have a very significant impact, however this proposal does not contain any studies that are likely to significantly advance development of the therapy that is already in Phase 1.
GWG Votes	**Is the rationale sound?**
Yes: 5	• The drugs to be used are already in the clinic, this is a repurposing of the drugs.
No: 7	• There is no clear rationale for this body of work. The Phase 1 study will be performed at a different institution and no new IND will be necessary for the Phase 2. The Phase 2 study should treat all and use the biomarkers to correlate with response. • The group already has an IND approved for this study. The Phase 2 study dosing will be based on the results of the Phase 1 trial. • An IND and Phase 1 trial are already being done at another institution. The applicant indicates they would like to perform a Phase 2 trial in California and that the Phase 2 trial will use the exact same intervention approved for the Phase 1 trial, except that the doses of drugs will be "determined based on the Phase 1 study results." The proposal therefore contains no sound rationale for how the proposed studies will improve the Phase 2 study.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 0	*none*
No: 12	• The proposal does not explain how the data will be used to achieve a meaningful outcome. • The experiments lack clear power calculations and data analysis plans thus rendering the approach uninterpretable. • It appears that the development of this therapy (Phase 2) can proceed without any of the proposed studies. As the FDA does not grant "pre-IND meetings for Phase 2", there is no need to show new laboratory data to the agency prior to Phase 2. • There is an existing IND ready for Phase 1 - the proposed studies do not substantially contribute to the initiation or design of a Phase 2 trial.
GWG Votes	**Is the proposal feasible?**
Yes: 4	*none*
No: 8	• The project may not be feasible during the timeline proposed. • The applicant will not be able to use this award to generate the necessary data for a pre-IND meeting, since there will not be a pre-IND meeting for Phase 2. It is not feasible to have an additional meeting with the FDA based on this proposal.

Application #	TRAN1-11042
Title (as written by the applicant)	Stem cell derived neuronal cell transplantation to repair the phrenic network after cervical spinal cord injury
Translational Candidate (as written by the applicant)	The translational candidate is a human stem cell derived source of progenitor motoneurons.
Area of Impact (as written by the applicant)	Targeted area of impact includes spinal cord injury, which results in devastating sensorimotor loss and dysfunction.
Mechanism of Action (as written by the applicant)	Transplantation of motoneuron progenitors into the injured spinal cord will combat injury by 1) secreting neurotrophic factors which will delay the loss of injured neurons, and 2) replace dying or dead motor neurons such that axonal growth from transplanted cells to the periphery leads to restoration of muscle function.
Unmet Medical Need (as written by the applicant)	Spinal cord injury results in permanent loss of strength, sensation, and movement below the level of injury. Injured individuals suffer from constant neuropathic pain. There are currently no existing treatments that can reverse or delay the resulting motor neuron death and devastating consequences.
Project Objective (as written by the applicant)	The proposal is aimed to achieve Pre-IND meeting.
Major Proposed Activities (as written by the applicant)	• Rodent studies to determine the optimal dose of cells necessary for functional respiratory benefits in a high cervical spinal cord injury model. • Rodent studies in a chronic model of cervical injury (1 month after injury; most relevant to clinical population) at the optimal dose of cells. • Rodent studies to test efficacy of pairing transplantation with task-specific rehabilitation to enhance transplant-host integration.
Statement of Benefit to California (as written by the applicant)	The proposed research will benefit the State of California and its citizens by accelerating stem cell treatments to individuals with spinal cord injury, for which there are no existing cures. Not only would the results of these studies have a positive impact on the scientific fields of stem cell therapy and traumatic spinal cord injury, but they will focus on individuals with unmet medical need.
Funds Requested	$2,057,487
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 scientific 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	• Cervical spinal cord injury (SCI) therapy is an unmet medical need. • Major unmet medical need for which there is no therapy. • Regenerative medicine for spinal injuries is a large unmet need. • Preclinical data may guide future large animal modeling and human clinical trials.
No: 7	• While this is an area of high unmet medical need, the plan will not have impact. The preclinical data are not directly supportive of the plan, and patient selection and clinical application are not realistic. • The proposed study will not have any impact. • The applicants need to show axon growth and muscle connection. • There are safety concerns that are not well addressed in the body of the application.
GWG Votes	**Is the rationale sound?**
Yes: 3	• There is strong rationale for targeting SCI. • Several initial preclinical studies were completed.
No: 12	• Intermittent hypoxia is not a pragmatic clinical intervention. • It is currently not safe to acutely expose high level cervical patients to intermittent hypoxia, nor to transplant them during the first month after injury. • The technology to inject cells at the site of spinal cord injury is rudimentary. • There is no evidence that grafts extend motor axons and form neuromuscular junctions with the diaphragm. • There are no data demonstrating that cells sprout axons which migrate to the diaphragm and develop a motor endplate in a setting which better simulates the human setting. • Axon growth and muscle connection needs to be demonstrated. • Proof of concept in terms of active phrenic motor neurogenesis e.g. axon formation is needed.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 2	• Generally well planned and designed.
No: 13	• Axon growth and muscle connection needs to be demonstrated. • Clear demonstration/characterization of a functional phrenic neuron is needed. • There are concerns with the potency of the motor neurons in the proof of concept. • A large animal model is needed. • Justification of dose is needed. • Need to demonstrate efficacy of intermittent hypoxia alone in this patient population. • The team needs input with clinical translation. It is not likely to transplant cells 30 days post injury, for example.
GWG Votes	**Is the proposal feasible?**
Yes: 5	• Strong investigators. • Excellent team and manufacturing capabilities. • The project would require further pre-clinical data (in vivo, large animal) and needs a practicing, research-oriented clinician to assist team on clinical feasibility (like intermittent hypoxia).
No: 10	• The study has a great team. • A strong contingency plan is presented. • This is not a project that can make a long dendritic process to replace phrenic nerve. • Good team, but the proposal needs work. Translation to humans may be an issue. • The clinical plan is not feasible at the present time. • Currently, the paradigm would not fit with safe clinical practice in weaning subjects from ventilation. Acutely injured high level subjects have not yet been tested with intermittent hypoxia.

Application #	TRAN3-11055
Title (as written by the applicant)	Transvascular access and aspiration of thoracic duct lymph for progenitor cell harvest and infusion.
Translational Candidate (as written by the applicant)	A novel catheter-based approach to aspirate and infuse large numbers of cells from the circulating lymphatic system
Area of Impact (as written by the applicant)	Collecting cells for T-cell and dendritic cell-based applications is time consuming, expensive, and provides low numbers of viable cells.
Mechanism of Action (as written by the applicant)	Our device provides a method for collection and infusion of large numbers of cells directly to and from the circulating lymphatic system. Once in place, the catheter may be used over weeks to months for chronic aspiration, infusion, and monitoring.
Unmet Medical Need (as written by the applicant)	Interest in cell-based therapies for a variety of disease states is at an all-time high. Access to a significant number of substrate cells remains a significant obstacle. The low number of desirable cells in blood makes ex-vivo expansion and manipulation difficult in a point-of-care setting.
Project Objective (as written by the applicant)	Pre-IDE meeting and manufacturing transfer
Major Proposed Activities (as written by the applicant)	• Product requirements and concept selection of a device suitable for long-term use • Large animal studies to verify usability • Verification and validation required for FDA approval
Statement of Benefit to California (as written by the applicant)	We are a CA-based company where design and manufacturing are performed entirely on-site at our CA facility. The proposed research will advance current research and provide a much needed therapeutic tool as well as add high-quality jobs in CA as the company progresses through manufacturing and clinical use.
Funds Requested	$1,886,238
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

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 scientific 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: 1	*none*
No: 13	• It is unclear what the unmet medical need is. • The clinical utility or bottleneck that is solved by the device is not clear.

	• There is no evidence that the device will provide any advantages over apheresis and the need for infusion directly into the lymph system (via catheter) has not been demonstrated. • The clinical application is not clear and advantages over current devices is not clear. • There is no obvious advantage over current apheresis methods. • The advantages of using this source of cells are not adequately described.
GWG Votes	**Is the rationale sound?**
Yes: 4	• The rationale is sound for the development of the device, but not for ultimate clinical use. • Very limited data shows some potential the device will work in people. • The animal model does not prove that the device works as intended, as you are not going into the lymph system, which will have very different properties than the venous system.
No: 10	• It is unclear what the rationale is for developing this device. • The study is not justified as the unmet medical need is unclear. • There is no obvious advantage over current apheresis methods. • The submission speaks to a validated pig animal model. The basis of validation is unclear. In any case, this model should be discussed with FDA as to whether or not they consider it appropriate for the catheter's intended use.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 5	• The project plan is appropriate for development of a medical device (catheter). The team has identified the major testing that would be needed to support either an IDE or a 510(k) submission. • The milestones are logical. • The use of the femoral vein model is questionable. • Substantial work has been completed, but this work isn't sufficient to overcome the lack of need for the device.
No: 9	• The pig model is not suitable anatomically, vein vs. lymphatic. • The animal model does not reflect potential clinical application. • It is unclear whether there was any approval to use human test subjects in another country.
GWG Votes	**Is the proposal feasible?**
Yes: 9	• Based on the preliminary data there is evidence that the proposal will work.
No: 5	• The regulatory risk has not been adequately addressed, i.e., identifying whether or not a clinical study will need to be conducted and addressing the costs associated with that study(s). • Overall, the project milestones and outcomes are feasible. However, it is unclear whether or not the devices to be used for the testing will be manufactured using 3D printing or using higher throughput manufacturing techniques. The team needs to be aware that the devices used for the testing must be representative of the devices that will be offered for sale. • Not a feasible study and will likely never go into clinical practice.