TRAN AWARDS 10/18/18

$13,478,286 GWG RECOMMENDED

$15,842,345 AMOUNT AVAILABLE

APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Resubmission	Previous CIRM Funding	Disease Indication	Product Type	Approach
TRAN1-11265	**Clinical Translation of Autologous Regenerative Cell Therapy for Blindness**	**$5,068,026**	**Y**	**85**	86	2	80	90	13	1	N	N	Retinal diseases	Cell therapy	Autologous iPSC-derived retinal progenitor cell transplant
TRAN1-11259	**Developing engineered autologous leukemia vaccines to target residual leukemic stem cells**	**$4,171,728**	**Y**	**85**	84	3	75	86	10	3	Y	N	Acute myelogenous leukemia (AML)	Biologic	Autologous genetically-modified AML vaccine targeting cancer stem cells
TRAN1-11300	**A purified allogeneic cell therapy product for treatment of Dry Age-related Macular Degeneration**	**$4,238,532**	**Y**	**85**	84	5	70	90	12	3	N	N	Age-related macular degeneration	Cell therapy	Allogeneic neural stem cell transplant
TRAN1-11305	**Human Amniotic Fluid Stem Cell derived Extracellular Vesicle for the treatment of Alport Syndrome**	**$4,809,020**	**N**	**80**	82	3	78	86	4	9	Y	Y			
TRAN1-11282	**Pre-clinical development of a small molecule for the treatment of osteoarthritis**	**$2,778,385**	**N**	**80**	80	4	75	86	1	12	Y	Y			
TRAN1-11322	**cGMP-grade placental stem cell production and characterization for treatment of congenital metabolic disorders**	**$5,417,153**	**N**	**75**	76	4	70	84	0	13	Y	Y			
TRAN1-11308	**HSC-Engineered Off-The-Shelf iNKT Cell Therapy for Cancer**	**$5,960,186**	**N**	**75**	74	4	70	80	0	13	N	Y			
TRAN1-11249	**Allogeneic human macrophage therapy for the treatment of complicated Intra-abdominal Infections (cIAI)**	**$3,050,571**	**N**	**70**	67	7	50	75	0	13	N	N			
TRAN1-11312	**A novel small molecule for borderline resectable pancreatic cancer.**	**$1,993,280**	**N**	**-**	-	-	-	-	0	13	Y	N			
TRAN1-11313	**Therapeutic development of human preterm umbilical cord derived mesenchymal stem cell conditioned medium for neonatal chronic lung disease**	**$3,740,602**	**N**	**-**	-	-	-	-	0	13	N	N			
TRAN4-11271	**Development of tumor microenvironment specific platform for the multiparametric spatial analysis of cancer tissues**	**$1,044,683**	**N**	**-**	-	-	-	-	0	13	N	N			

Application #	TRAN1-11265
Title (as written by the applicant)	Clinical Translation of Autologous Regenerative Cell Therapy for Blindness
Translational Candidate (as written by the applicant)	We are studying autologous induced pluripotent stem cell-derived retinal pigment epithelium cells for the treatment of maculopathies.
Area of Impact (as written by the applicant)	Maculopathies (including AMD, SMD, & MMD) may be treated with cells to replace RPE and support photoreceptors to improve vision.
Mechanism of Action (as written by the applicant)	Autologous induced pluripotent stem cell-derived retinal pigment epithelium cells replace RPE lost to disease, and support continued photoreceptor function. Transplanted cells perform functions of the RPE layer: providing a membrane between the neuro-sensory retina and the choroid permeable to ions and metabolites; phagocytosis of photoreceptor outer segments; synthesis of Bruch's membrane matrix; light absorption and improving image resolution. By performing these functions, the cells support photoreceptors, improving vision.
Unmet Medical Need (as written by the applicant)	Disorders affecting the macula cause loss of central vision and disability. Maculopathies affect will affect ~20M people in the US by 2020. There are no approved treatments for these conditions. Patient specific stem cell derived retinal pigment epithelium (RPE) cells provide a potential treatment.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Cell therapy product generation and formulation (7 replicates) • Qualification of assays for manufacturing process, development and optomization of in-process and release potency tests • Preclinical testing of safety and efficacy
Statement of Benefit to California (as written by the applicant)	About 800,000 Californians had vision related disorders in 2016, a significant subset of which are maculopathies caused by degeneration of retinal pigment epithelium cells. There are no effective treatments for most of these conditions. Development of effective therapies for multiple forms of maculopathy, supporting recovery of the damaged retina, would offer tremendous functional benefits to many residents of the State of California, and fiscal benefits from reduced long-term healthcare costs.
Funds Requested	$5,068,026
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	86
Median	85
Standard Deviation	2
Highest	90
Lowest	80
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	13
(1-84): Not recommended for funding	1

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. 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	• This disease affects more than 10% of the population over the age of 65, and includes age-related and myopic macular degeneration and Stargardt macular dystrophy (SMD). By 2020 nearly 20M people in the US will be affected by these conditions. Currently no treatments or cures are available to most of these patients. • If successful, this therapy will meet a clear and present need in an aging CA population, but it might be a very expensive treatment. • There is an unmet need for this therapy.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• This is an autologous therapy which is attractive. However, not all macular degeneration is due to retinal pigment epithelial cell deficiency. • The only concern would stem from using cells from a patient with a genetic disease but potentially it doesn't affect the iPSC. • An autologous fresh cell preparation may be challenging to move to commercialization in the future.
No: 1	• It is unclear whether the cells will go through a 38 gauge needle, although they will test this. • While the results of these studies have been encouraging regarding safety, none have demonstrated definitive signs of efficacy such as significant gain of vision.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 12	• A strong path toward the pre-IND is presented together with a strong safety program, resulting in a well-developed, impressive program. • The pre-pre-IND was very helpful to provide an accelerated path to a pre-IND which includes strong manufacturing, characterization and pilot data in vivo and in vitro.
No: 1	• It is unclear whether the therapy will translate to older individuals. The animal models are young and the injections occur early in the disease, but the study is designed to look at long-term effects. • Information on the current donors and more details about the animal studies is needed. It is unclear what the ages of the donors are, and how the age of the donor will affect the final product. It is also unclear whether they are comparing different cell sources when testing the donor cells in the animals models. • The applicants state that low doses have not worked, but it is unclear whether higher doses will work either.
GWG Votes	**Is the proposal feasible?**
Yes: 13	• This is a feasible, non-invasive therapeutic product. • Strong application; there is enthusiasm in regards to no immunosuppression and short procedure for the patient. • The fresh cell preparation limits some applications.
No: 0	*none*

Application #	TRAN1-11259
Title (as written by the applicant)	Developing engineered autologous leukemia vaccines to target residual leukemic stem cells
Translational Candidate (as written by the applicant)	A 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 50%. However, the vast majority of these individuals relapse within a year due to the persistence of residual AML and leukemia stem cells. Our 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 stem cells. Vaccination after remission could increase relapse free, and even overall 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 we can eradicate leukemia in preclinical models by treating with AML vaccines, engineered to more effectively stimulate anti-leukemic immune responses.
Project Objective (as written by the applicant)	Submit Pre-IND package and 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 chemotherapy, creating financial and geographic challenges. Despite this therapy, most patients relapse. We propose a powerful strategy for converting patients' leukemia cells into effective vaccines that stimulate anti-leukemic immunity. Outpatient treatment with genetically engineered AML vaccines may be an effective strategy to decrease relapse by boosting anti-leukemic immune responses post-remission.
Funds Requested	$4,171,728
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	84
Median	85
Standard Deviation	3

Highest	86
Lowest	75
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	10
(1-84): Not recommended for funding	3

KEY QUESTIONS AND COMMENTS

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GWG Votes	**Does the proposal have the necessary significance and potential for impact?**
Yes: 13	• AML is a major unmet need and novel immune-based therapies for AML are needed. • Novel therapies such as this vaccine are needed in advanced/relapsed AML. • In addition to improving patient outcomes, the possibility of an autologous dermal vaccine treatment is attractive. • The concept of targeting leukemia stem cells (LSC) is of increasing interest. • If a patient's immune system, especially after chemotherapy, can still be redirected to target their leukemia, this could have a significant impact on their disease.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 11	• A concern raised previously was whether actual patient AML starting material, especially after chemotherapy, would be capable of mounting a sufficient immune response. In this new submission, the applicants have provided additional pre-clinical data that suggests immune responses can be detected in this setting. The new pre-clinical data, along with reported preliminary results from other similar vaccination clinical studies, supports further development of the product. • Overall, immunotherapy-based targeting strategies are a sound approach. Whether vaccination strategies can achieve sufficient immune responses to actually impact clinical outcomes still needs to be demonstrated. • The ultimate utility of the product remains unclear. However, this will be sorted out in the clinic. • It is unclear whether the product will break the immune tolerance. It is likely it will take a combination of therapies, but one needs to start somewhere. • Overall, the data support development of the product as an anti-cancer therapy. There remains, however, a gap in supporting this as a stem cell-targeting product. • The generation of the vaccine is feasible.
No: 2	• The mechanism of therapeutic benefit is unclear, and whether an immune response will be generated in the post-chemotherapy setting if LSC are not targeted by vaccine. • It is still not clear whether this would work in patients who have received immunosuppressive therapy. • The rationale of including an immune response to LSC is a strength.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 11	• The studies are well suited for the pre-IND meeting. • The applicant has continued to move this program forward since the initial submission, and the preclinical and regulatory tasks defined are appropriate.

No: 2	• The applicant response to the previous review did not adequately address the two fundamental concerns:
	  ◦ Additional preliminary data are needed to support efficacy.
	  ◦ It is unclear whether using bulk leukemic cells for vaccine generation adequately targets LSC.

GWG Votes	Is the proposal feasible?
Yes: 13	● A good effort was made to improve the proposal. ● The product will be made and is likely to be approved by FDA. ● While generation of the PDX models may fail, the program overall is positioned to achieve a meaningful pre-IND meeting if other tasks encounter problems. ● The technical expertise of the team is good. ● Excellent team.
No: 0	*none*

Application #	TRAN1-11300
Title (as written by the applicant)	A purified allogeneic cell therapy product for treatment of Dry Age-related Macular Degeneration
Translational Candidate (as written by the applicant)	An allogeneic cryopreserved neural stem cell therapy product
Area of Impact (as written by the applicant)	Dry Age-Related Macular Degeneration (AMD)
Mechanism of Action (as written by the applicant)	Similar to RPE cells, these cells restore phagocytic function to the retina, secrete anti-inflammatory and trophic factors (VEGF and BDNF), maintain retinal integrity and prevent vision decline. Cells migrate radially from transplant site, self-renew to produce more cells and stimulate proliferation of endogenous host RPE cells. These properties allow the implanted cells to exert protective effects over larger target areas and could potentially restore areas of geographic atrophy.
Unmet Medical Need (as written by the applicant)	AMD is the leading cause of irreversible vision loss in people over 60 in the US with no effective therapies. AMD incidence is rapidly increasing as the average age of the population increases. These cells will halt the process (slow progress, revision, etc) of vision loss.
Project Objective (as written by the applicant)	Successful Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Manufacturing process changes for more consistent and better procedural delivery of the product. • Animal study to confirm dose, delivery instrument and local immunosuppression regimen achieving >50% of eyes with product. • Alignment with FDA on successful path to Phase 2 IND for geographic atrophy in AMD.
Statement of Benefit to California (as written by the applicant)	Dry age-related macular degeneration (AMD) is the most prevalent retinal degenerative disorder and represents a significant unmet medical with no therapy to slow progression or cure this debilitating disease. In California, a 2014 analysis estimated the cost due to vision loss and blindness at $7,592M and $8,054M respectively. These cells have preliminary evidence of efficacy and proposed changes should enhance patient access, commercial viability and accelerate the path to market.
Funds Requested	$4,238,532
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	84
Median	85
Standard Deviation	5
Highest	90
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	12
(1-84): Not recommended for funding	3

KEY QUESTIONS AND COMMENTS

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GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 12	• If successful, this product would be helpful to many people. • There is a medical need for new therapy for AMD. • This is an interesting and useful application of a human neural stem cell line for an unmet need in CA. • A lot of therapies in development are targeted to only one protein (antibodies or gene therapies), whereas this approach could be more successful in slowing the degeneration of RPE tissue.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• The rationale for repopulating retinal pigment epithelium from allogeneic cells (neural stem cell) via transplantation has sound preliminary data. • In addition to the preliminary clinical data, the applicant has demonstrated efficacy in robust studies in the RCS rat model. Mechanistic studies in this model support the rationale for this approach. The studies in the preclinical model appeared to raise challenges specific to the species that would not be expected in humans. • An implant for treating macular regeneration is rational; the cells will need to be formulated very carefully. • There are potential problems of immunosuppression of older recipients, though there is some existing clinical and regulatory experience with a different formulation of these cells.
No: 1	• The animal studies have a very small 'n'. Work is needed to determine dose, timing, how often to repeat the therapy. It is unclear how the stage of the disease impacts the dosing and efficacy. • It is unclear what the viability of the product will be through the 38 gauge needle.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 12	• The milestones are well conceived and the approach is well-planned; concerns about clusters vs single cells seem resolved. • This is an accelerated development plan based on the existing clinical data with the 'cell clusters'. However the applicants have a thorough plan for ensuring the program moves forward without new safety risks to patients. While the applicant aims to move into phase 2 with the new IND, this does not appear overly aggressive and they have consulted with regulatory experts on the best path forward. • The applicants will make use of data from previous IND studies where applicable. • It is unclear if there will be ongoing access to the original master cell bank. • There is no mention of possible off-site migration.
No: 1	• The idea is to remove the cell clusters and create a single cell suspension. The old therapy seems to work, but it is unclear whether the single cells are better. A little more data is needed. It might be that clumps are better. It is unclear whether the single cells will attach and work in the same way, or if they will they all leak out.
GWG Votes	**Is the proposal feasible?**
Yes: 13	• The injection of single cell suspension may be technically difficult; there is concern about other, unrelated effects of the cells. • It is unclear whether a new cell bank or single cell line is needed. • The application identified appropriate contingencies for 3 risks (failed large animal study, failed rat study, and failed WCB production). It is not clear how the applicant will move forward if the new immunosuppression regimen does not appear to work, but the cell therapy itself could potentially still be developed for a smaller population.

	• The amount of capital equipment requested is significant. • Appropriate expertise and facilities are available.
No: 0	*none*

Application #	TRAN1-11305
Title (as written by the applicant)	Human Amniotic Fluid Stem Cell derived Extracellular Vesicles for the treatment of Alport Syndrome
Translational Candidate (as written by the applicant)	Human Amniotic Fluid Stem Cell derived Extracellular Vesicles (hAFSC-EVs) with renal-protective activity.
Area of Impact (as written by the applicant)	hAFSC-EVs would treat glomerular sclerosis in patients affected by chronic kidney disease, like Alport Syndrome for which there is no cure.
Mechanism of Action (as written by the applicant)	Our goal is to develop an effective therapy to treat patients that suffer from Alport Syndrome, a chronic kidney disease. We propose to use human amniotic fluid stem cell-derived extracellular vesicles (hAFSC-EVs) as a new product for the treatment of glomerular sclerosis. hAFSC-EVs can be considered "off the shelf" product that, once injected, can restore normal glomerular function by regulating glomerular cellular cross-talk, thus delay/reverse the progression of chronic kidney disease.
Unmet Medical Need (as written by the applicant)	There is no effective treatment to slow or halt the progression of chronic kidney disease. hAFSC-EVs will slow or halt the progression to end-stage renal disease is Alport Syndrome patients. This will improve the patients quality of life and delay kidney transplantation.
Project Objective (as written by the applicant)	Effective Pre-IND meeting with FDA.
Major Proposed Activities (as written by the applicant)	• Manufacturing process development and generation of lots of hAFSC-EVs to support Phase 1 and Phase 2 trial. • Performing efficacy, toxicity and safety studies in pre-clinical animal models of Alport Syndrome. • Collection and evaluation of all data for the Pre-IND meeting with the FDA.
Statement of Benefit to California (as written by the applicant)	The State of California spends yearly millions of dollars in dialysis treatments and in kidney transplants. Our child and adult patients will greatly benefit from a tolerable, safe but most importantly effective therapy preventing renal failure. California will benefit from the high reduction in medical costs, and this discovery will place the state as one of the major centers in the nation for the treatment of this devastating disease, which ultimately will contribute to economic growth.
Funds Requested	$4,809,020
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	82
Median	80
Standard Deviation	3
Highest	86
Lowest	78
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	4
(1-84): Not recommended for funding	9

KEY QUESTIONS AND COMMENTS

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GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 13	• Potentially transformative; there is a clear unmet need. • Alport disease is a significant unmet medical need. • Alport is a rare genetic disease with poor prognosis and reduced life expectancy.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 10	• There is promising preliminary data on a protective effect of the EVs. • An EV-based therapy is rational but knowledge of the biology of EVs is critical. • More science is needed to drive it forward. The MOA is unclear. It is unclear whether the EVs are really better than cells. • The animal studies are well developed and thought out. • The proposed 'n' is too small for the large animal study and funding to obtain additional animals will be hard. So as much information as possible from the rodent studies will need to be translated. The dose, stage of the disease, whether EV are better than cells, are all important to determine in mice. It is unclear whether VEGF is the only mechanism. An additional mouse model which may have other co-morbidities available may better inform the large animal studies. • Dose finding in mice would be helpful, since the applicants are testing different stages of disease.
No: 3	• The mechanism and approach may extend to larger population.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 9	• The applicant addressed previous review comments. • Most of the studies are well thought out. Testing against the current and in conjunction with the current standard of care is very important. There is a question of how long the therapy will prolong the time to transplantation. • Better characterization of the product is needed. The planned experiments should yield useful information. • It is unclear whether the large animal study with so few animals will yield significant results (dosing, etc) to the warrant cost. • The production of EVs for therapy is a concern. • The applicants should work towards serum-free manufacturing.
No: 4	• The murine AS model dose-finding studies could provide valuable information, especially as such results might also relate to treatment at different stages of disease which is being proposed for testing. There may be a dose response relationship between stage of disease and number of EV needed for therapeutic benefit. This will be much easier to assess in the murine model, although confirmatory studies in the large animal model would be valuable. • There is some concern whether allometric scaling will be appropriate for both the animal model and for human clinical studies. • Biodistribution studies should also include some controls using standard IV infusion to further assess the requirement for the proposed intracardiac injection pathway. • For better characterization of in-process and final products, instead of using %+ for EV (ex. Fig. 16), the mean fluorescence intensity (MFI) should be reported along with coefficient of variation (CV) for each of the proposed markers. • Intensity/distribution of surface antigens will be a better descriptor of EV population heterogeneity than a simple +/- % designation. • Scaling the therapy is complicated.

GWG Votes	Is the proposal feasible?
Yes: 11	● There are potential risks (derivation of new donor AFSC parent line, master and working cell bank generation, scale-up manufacturing, etc.) that are likely to impact timeline and milestones. ● The manufacturing needs improvement. ● Manufacturing needs to be defined. ● More regulatory input and a focus on GMP production technologies is needed. ● It is unclear whether EV have specific migratory principles. ● Expert team.
No: 2	*none*

Application #	TRAN1-11282
Title (as written by the applicant)	Pre-clinical development of a small molecule for the treatment of osteoarthritis
Translational Candidate (as written by the applicant)	A novel small molecule drug candidate
Area of Impact (as written by the applicant)	The drug will be targeted to prevent the advancement of, or reverse, osteoarthritis
Mechanism of Action (as written by the applicant)	This drug protects a patient's own cartilage stem/progenitor cells, shielding them from signals that would overstimulate them and cause them to degrade the cartilage around them. Because of this, this drug may interrupt the disease cycle and allow cartilage stem/progenitor cells to repair cartilage damage. These changes in the joint should reduce pain and increase mobility in treated patients.
Unmet Medical Need (as written by the applicant)	25 million adults suffer from osteoarthritis. Beyond reducing pain, there are no current treatments that slow or stop the progression of osteoarthritis. This drug could become the new standard of care by slowing or reversing osteoarthritis (OA), positively impacting the lives of millions of adults.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Rodent studies to optimize dosage amount and route of adminstration • Toxicity studies in rodents and dogs to verify safety of the drug • Testing doses in a dog model of OA immediately and some time after injury to assess efficacy in FDA-required large animals
Statement of Benefit to California (as written by the applicant)	5.9 million Californians suffer from arthritis. Currently, treatments for osteoarthritis focus on pain management, only treating the symptoms of the disease. This drug protects cartilage stem/progenitor cells, making them resistant to degenerative signals and potentially helping them repair cartilage damage. Therefore, this drug could be the first treatment to interrupt the disease cycle in OA, potentially changing the lives of millions of Californians by reducing pain and increasing mobility.
Funds Requested	$2,778,385
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	80
Median	80
Standard Deviation	4
Highest	86
Lowest	75
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	1
(1-84): Not recommended for funding	12

KEY QUESTIONS AND COMMENTS

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GWG Votes	**Does the proposal have the necessary significance and potential for impact?**
Yes: 13	• This proposal has tremendous opportunity - OA is a huge clinical problem with no obvious solution. • There is a massive unmet need for this ubiquitous disease. • This drug could become the new standard of care by slowing or reversing OA, positively impacting the lives of millions of adults. • The applicants did an impressive job in an attempt overcome the previous issues of Myc. • The disease modifying strategy of this compound is attractive, and a large medical need exists.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 9	• The rationale is sound and would be consistent with other models out there. • Well-organized and presented proposal. • Good preliminary data based on animal models. • The dual mechanism approach is sound.
No: 4	• The immediate and delayed dosing data is helpful, but no aged animals are used, so it is still unclear whether this will work in the target population. The drug might be better for a younger population as a preventive measure. However, it would have to be very safe, well-tolerated, and the endpoints would be very difficult to measure. • The limited data available supports the further development of the product. However, the tumorigenic potential of the clinical candidate, based on its mechanism of action, is a concern. Although the drug was demonstrated to affect both the MYC and STAT pathway to a lesser extent than its structurally similar analogues, the effect of the drug metabolites on the proliferative pathway (Myc and Stat) have not been considered. • It is unclear whether the metabolites of the new analog will these have same issues with Myc; experiments to test this are needed. • It is unclear whether this is a stem cell therapy.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 8	• Generally good response to points raised in previous review. • The proposal is well planned - particularly with respect to the study including the large and small animal model as well as the oral and intra-articular dosing. • The new molecule with similar therapeutic mechanism to the original apparently has much lower toxicity/tumorigenic potential, but a more direct assessment of potential for tumorigenicity is needed. • There is concern about the potential toxicity of metabolites - this needs to be evaluated. • In the safety/toxicity testing, monitoring of CV arrhythmias is suggested.
No: 5	• More information is needed in regards to risk mitigation, particularly as this drug will be administered for long periods. • There are concerns about carcinogenic effects that are not adequately addressed, and also issues about immunogenicity. • More toxicology studies are needed. • I appreciate that the team has enlisted a safety expert to design the preclinical package. However, there is concern with the lack of studies on the tumorigenic potential of the clinical candidate. Prior to the pre-IND meeting it is advised that the investigators conduct at least one in vitro cell transformation assay to define the tumorigenic potential of the clinical candidate.
GWG Votes	**Is the proposal feasible?**
Yes: 10	• The project is feasible but the tumorigenicity issue must get worked out.

	● This product has significant merit if the applicant can risk mitigate the tumorigenic potential of the drug and its metabolites. ● This project is ambitious with some difficulty overcoming the delayed presentation of OA in humans vs, the in vivo animal disease models. ● More preclinical data is needed. ● Ambitious timeline. ● Good institutional support.
No: 3	● There are concerns about the timeline.

Application #	TRAN1-11322
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)	• Obtain proof-of-concept data with adult MPS-1 mice • Isolate hAECs with a clinically applicable protocol under cGMP conditions • Evaluate the quality and therapeutic potential of isolated cells
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	$5,417,153
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	76
Median	75
Standard Deviation	4
Highest	84
Lowest	70
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. 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: 10	● This project addresses a novel treatment for mucopolysaccharidosis type 1 (MPS-1) disease, by transplantation of human amniotic epithelial cells (hAECs). If the treatment is effective, there is a high potential for impact and reduced costs, with a major benefit to patients. ● The cell population is an interesting one. It may have utility in these rare diseases, but its not clear that MPS-1 is the best choice. ● There is a need for novel therapies to replace transplantation or enzyme therapy.
No: 2	● The project addresses a rare genetic disease.
GWG Votes	**Is the rationale sound?**
Yes: 3	● The animal studies are reasonable as a model, but the transition to the clinic is still not well worked out.
No: 9	● The rationale for claiming potential efficacy is that previous studies have shown that transplantation of mouse AECs can lead to increases in enzyme activity up to levels of 25% of normal in the liver. Studies published last year were interpreted to show that these transplants in a mouse model cause decreased GAG accumulation in the phalanges joints and the composition and morphology of cranial and facial bones. There was also reported improvement of sensorimotor function. However, this same report states that increases of enzyme activity were not significant in kidney, lung, spleen, heart or brain. Staining of stratum, cerebellum or kidney showed only minor decreases in GAG levels. There are statistically significant decreases in bone density, but they are small. In addition, differences in ease of mobility were not quantified. ● Improvements in rotarod performance were interpreted as being associated with improved learning and motor performance, but no other tests were performed and there are other possible interpretations of the data. In particular, improvement in activities like this may not necessarily have anything to do with cortical learning. Moreover, these analyses represent single analyses conducted over the span of five days and the improvements seen at each time point are exaggerated by the graphic representation provided in the grant application. ● There is no evidence this therapy is better or more efficacious than HSCT or enzyme therapy. ● The pre-clinical data is not very compelling. ● The pre-clinical efficacy data may be overstated and over-interpreted which raises concerns.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 3	● The animal POC studies are feasible and well designed. However, the clinical implementation for this therapy is quite vague, and the advantage of this approach over and above the existing therapies was not well stated.
No: 9	● There appears to be a strong over-interpretation of data in the publication from this group, and this paper appears to provide the only preliminary data on the value of this approach. Thus, there is a reasonable concern that efficacy in the context of providing clinical value remains only theoretical. ● The proof of concept offered is extremely limited. The applicants state the primary goal is restoration of enzyme activity in the liver, evaluation of GAG levels and bone, and analysis of enzyme activity in the brain. Information is not provided, however, on what will be considered successful outcomes. This appears to be a problem throughout the POC studies. Moreover, the published studies show only limited benefit in the brain in the limited studies conducted. ● There are many issues with the animal models, durability, route of admin, dose, amount and timing and frequency. These have not be well-addressed in the response to the previous review. ● The outcomes that will be considered as effective in the POC studies are poorly defined, making it difficult to evaluate whether the proposal is well designed. ● The authors note that neonatal mouse transplantation is problematic for multiple reasons, which is why proof of concept studies are being moved to older mice. However, it is the younger mice that are the appropriate model. Transplantation at the age of 3-4 weeks of age would more closely resemble the window targeted in humans, which would be transplantation prior to 2 years of age. ● More information is needed. There is vague dosing information on POC study 2 as it appears there may have been multiple doses but the time between doses or the total number are not discussed.

	● Manufacturing is a significant issue, as is HLA matching. This may not be a deal breaker, but the HLA distribution of the patient population may have a significant impact on the success of the proposal. ● The plans for transitioning the therapy to the clinic are not clear.
GWG Votes	**Is the proposal feasible?**
Yes: 9	● The pre-clinical experiments and toxicity studies are feasible. However, the rationale for its clinical usefulness has not been made in MPS-1. ● The time line is reasonable. ● The cells are easy to produce
No: 3	● The proposal is technically feasible, but evidence is lacking as to whether this approach has feasibility with respect to therapeutic outcomes. References to other diseases that do not represent problems in GAG deposition are of only limited relevance to the disease intervention proposed. ● Risks are not well identified. For example, the applicants have not discussed the risks if the therapy doesn't work in adult mice, has short durability, or partly works, ie. improves urine parameters but not neurological issues.

Application #	TRAN1-11308
Title (as written by the applicant)	HSC-Engineered Off-The-Shelf iNKT Cell Therapy for Cancer
Translational Candidate (as written by the applicant)	Allogeneic HSC-Engineered HLA-Negative Human iNKT Cells
Area of Impact (as written by the applicant)	Cell-based immunotherapy for cancer have shown great promise. Allogenic immune cellular products are in great demand for treating cancer patients.
Mechanism of Action (as written by the applicant)	The proposed HSC-engineered off-the-shelf iNKT cellular product can be readily administrated into cancer patients through i.v. infusion. These therapeutic immune cells have a remarkable capacity to target a broad range of cancers independent of tumor antigen- and MHC-restrictions. They also can employ multiple mechanisms to attack tumor cells through direct killing and adjuvant effects. Therefore, the product can potentially be used to treat multiple cancers and a large population of patients.
Unmet Medical Need (as written by the applicant)	Novel therapies for treating cancer are in great demand. The proposed HSC-engineered off-the-shelf iNKT cell therapy has the potential to become a general cancer immunotherapy for treating multiple cancers and a large population of cancer patients.
Project Objective (as written by the applicant)	Pre-IND meeting with the FDA.
Major Proposed Activities (as written by the applicant)	• Conduct pharmacology studies of the cell product • Conduct CMC studies of the cell product • Conduct pilot safety studies of the cell product
Statement of Benefit to California (as written by the applicant)	Cancer affects tens of millions of people worldwide and is a leading threat to public health in the United States and in the State of California. It is the second leading cause of death in California, resulting in more than 56,000 deaths each year, and also brings devastating economic impacts to the state. The proposed HSC-engineered off-the-shelf iNKT cell therapy has the potential to treat a large population of cancer patients, therefore can benefit the state of California and its citizens.
Funds Requested	$5,960,186
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	74
Median	75
Standard Deviation	4
Highest	80
Lowest	70
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. 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: 11	• Most tumors still cannot be treated with cell therapy because of lack of good targets or immune suppression. This iNKT approach may broaden the number of tumors that could be treated. • iNKT cells are an interesting approach, affordable, off-the-shelf, and may have anti-cancer activity. • The anti-cancer effects of the cells, especially available off-the-shelf, is therapeutically attractive. • Current immunotherapies struggle to avoid GVHD as a treatment side effect, also treatment-related toxicities and risk of relapse remain major challenges with current cancer treatment modalities.
No: 2	• It is difficult to determine the potential of this therapy at this point as the preliminary data is not compelling on direct tumor killing. • Despite some published information on NK cell therapy for cancer, it is not clear how effective this could be on its own or in combination with other therapies.
GWG Votes	**Is the rationale sound?**
Yes: 5	• This therapy is likely most beneficial in combination therapy applications. Those need to be included in pre-clinical studies. • Pre-clinical data from animals show ~30% reductions in tumor burden.
No: 8	• The preclinical data is not very strong, showing minimal efficacy on it own. It could be perhaps be strengthened in preclinical experiments showing synergistic effects with other cell types and/or therapies. • The data as submitted appears to show only a minimal degree of clinical effectiveness using high cell doses with optimized tumor targets. It is unclear whether this will translate well into the clinic. • Additional pre-clinical efficacy studies may be helpful at this early stage of development. • Given the limited anti-tumor activity in the preclinical models, it is important to provide additional mechanistic data. For example, what happens with regards to cytokine expression upon activation and the outcome of engagement with DCs is needed. • The anti-tumor effects are not clearly understood. • The evidence of specific anti-tumor targeting is unclear.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 4	• It is likely that iNKT cell therapy will have to be combined with other therapies to be effective. This possibility should be considered at this point so it can be incorporated into early clinical studies as well. • The manufacturing needs to be more sophisticated e.g. use of closed systems and bioreactors, and if possible needs to be simplified.
No: 9	• More pre-clinical proof of concept and demonstration of effectiveness is needed. • More detail is needed on in vivo studies, no 'n' values are indicated. • The complicated manufacturing process is a concern. • The potential need to re-create the ATO cell line is a concern; the ability to comply with cGMP regulations with the current cell line is critical in rapidly moving this technology forward. • There could be significant CMC issues when scale-up is attempted.
GWG Votes	**Is the proposal feasible?**
Yes: 9	• A closed manufacturing system is recommended instead of simply scaling in 150 cm2 flasks so it's ready for broader use following early success. • Scale-up of these cells appear to be a significant hurdle. • A budget of $960 per mouse is confusing. It is unclear what this includes but it appears to be just the cost of the mouse.

	• Strongly recommend a pre-pre-IND meeting as soon as possible, but certainly before conducting IND enabling animal studies. • Good team and facilities.
No: 4	• The project would not be ready for a pre-IND meeting. • There are concerns about scale-up and ATO cell line qualification.

Application #	TRAN1-11249
Title (as written by the applicant)	Allogeneic human macrophage therapy for the treatment of complicated Intra-abdominal Infections (cIAI)
Translational Candidate (as written by the applicant)	An allogeneic macrophage cell therapy product derived ex vivo from pluripotent blood cell progenitors.
Area of Impact (as written by the applicant)	Complicated intra-abdominal infection (cIAI), a common and serious bacterial infection impacting 250K patients a year in the USA.
Mechanism of Action (as written by the applicant)	This product is an ex vivo derived allogeneic macrophage cell therapy that will function in concert with standard of care to treat cIAI. Macrophages are linchpins of the innate immune system, engulfing and destroying pathogens and releasing factors that attract and stimulate other immune cells. This combination of direct bacterial cell killing and indirect immune cell recruitment by the macrophage cells will result in decreased morbidity, mortality and healthcare costs in cIAI .
Unmet Medical Need (as written by the applicant)	cIAI is a common infection affecting ~250K patients a year in the USA with an overall mortality rate of 10%. The standard of care is less effective in older patients or those with co-morbidities, and drug-resistant bacteria are on the rise. Thus, novel broad-spectrum therapeutics are sorely needed.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Rodent studies to determine therapeutic dose/regimen, mechanism of action, biodistribution, and preliminary safety profile. • Demonstrate efficacy of cGMP material via in vivo and in vitro bacterial infection assays. • Pre-IND submission and correspondence with the FDA.
Statement of Benefit to California (as written by the applicant)	Drug-resistant infections are a serious problem leading to significant morbidity and mortality and increased healthcare costs for Californians – and they are on the rise. One such infection, complicated intra-abdominal infection (cIAI) is a common and serious condition with a 30% treatment failure rate due to age or underlying disease. This therapy has the potential to dramatically decrease the length of hospitalization and the risk of death and disability for Californians with cIAI.
Funds Requested	$3,050,571
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	67
Median	70
Standard Deviation	7
Highest	75
Lowest	50
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. 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	• This therapy would be helpful, but in many cases there are existing therapies that do work. • Abdominal infection is a costly, often intractable clinical problem. • The proposal has some potential but is at too early of a stage at this point. • Although preclinical studies have been vetted by the FDA, they may not be the best model to demonstrate proof of concept.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 1	*none*
No: 11	• It is unclear whether the therapy will really work in clinical setting. • A broad clinical indication is being proposed (e.g., heterogenous disease) which complicates the human clinical approach. It is unclear what the clinical approach would be, and this will have a large impact on the required pre-clinical studies to support clinical development. • The clinical indication is known to contain a diverse bacterial population (polyclonal microbes) and should be evaluated in a pre-clinical animal model that reflects the clinical environment. • The applicant uses an unusual MRSA mechanism for the animal model rather than a polymicrobial animal model, which is the more typical clinical scenario. • It is unclear how this therapy compares to antibiotics. • It is unclear whether the cells work well after freezing and thawing. • It is unclear whether the proposed numbers of cells would be sufficient for human therapy.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 2	*none*
No: 10	• The applicants demonstrate human monocyte-derived macrophages and mouse bone marrow-derived macrophages stimulated with IFN can kill gram-negative bacteria more efficiently than unstimulated macrophages in vitro. However, it is unclear what this would mean clinically. • Mouse cells demonstrated significant protection from lethal MRSA peritoneal infection in wild type mice relative to PBS control. However, it is unclear whether this is a true model of MRSA. Strong data from a poly-microbial infection model is needed. • The pre-clinical study design may be improved upon with more relevant poly-microbial animal models. • The in vivo studies need more detail. Other animal models might be better than the proposed models. • A larger animal model is suggested, which may help to inform spacial issues of a larger abdominal cavity. • Pre-clinical studies need additional groups to compare the therapy to the standard of care, e.g. other antibiotics. • The proposed study looks at dose and number of doses. The applicants should consider the timing of the dose. It is unclear how the therapy will work early in the disease vs. late. Placement of the dose is also a concern. • Cell manufacturing is a concern. It is unclear how many macrophages will be needed for each procedure, whether the macrophages will be active and able to phagocytose, and how many cell are needed for a therapeutic effect. • The freeze/thawing of the cells and preservation of cell viability is a concern.
GWG Votes	**Is the proposal feasible?**
Yes:	*none*

4	
No: 8	• If all other areas are appropriately addressed, then this project may be feasible to test and demonstrate clinical relevance. • As proposed, the project would not be ready for a pre-IND meeting in 18 months. • There are significant manufacturing scale concerns.

Application #	TRAN1-11312
Title (as written by the applicant)	A novel small molecule for borderline resectable pancreatic cancer.
Translational Candidate (as written by the applicant)	A novel small molecule
Area of Impact (as written by the applicant)	Clinical oncology/radiation treatment for pancreatic cancer
Mechanism of Action (as written by the applicant)	In the case of clinical treatment of pancreatic cancer with radiation and chemotherapy, small bowel toxicity occurs which is dose limiting to patients. This drug is intended to protect small bowel without protecting pancreatic tumor cells allowing patients who are borderline non-resectable for pancreatic cancer to be respectable via improving the ability to stay on therapy, reduce the number of breaks from therapy or eliminate therapy dose reduction of chemo and or radiation.
Unmet Medical Need (as written by the applicant)	There are no drugs that can prevent small bowel or epithelial toxicity to radiation and/or chemotherapy. Currently we do not deliver sufficient therapeutic doses of these to borderline resectable and locally advanced un-resectable pancreatic cancer patients to make a curative difference (low therapeutic difference).
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: gene tox, tox in 2 species, ADME and PD. • Key rodent studies introducing chemotherapy vs. just radiation to understand the drug 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 we have a vision 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	$1,993,280
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	13
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. 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	• There is a strong unmet need, but it is not clear if this therapy will fulfill this need. • There is an unmet need in pancreatic cancer; it is not clear that this approach contributes much. • The resubmission does not respond well to the previous review.
No: 5	• It is unclear what the impact would be for pancreatic cancer patients: how many would be helped, whether they would be able to complete radiation therapy, whether a higher dose of radiation is needed in these patients.
GWG Votes	**Is the rationale sound?**
Yes: 2	*none*
No: 11	• The applicants did not really address the previous critiques. It is still likely that other therapies might work better. • The rationale is not entirely clear; the rationale for the proposed experiments is not focused. • The signaling/cellular mechanism is not well supported. • The applicant should provide evidence of what the benefit to pancreatic cancer patients would be and how many could be helped if the symptoms of radiation toxicity are controlled by supportive care already. • The initial mouse experiments were with lethal doses of radiation, but pancreatic cancer patients are not being given a lethal dose. Thus, the rationale for what would be achieved in the clinic is confusing. • The rationale is confused with respect to use in lethal versus non-lethal radiation.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 1	*none*
No: 12	• The applicant did not address the previous critiques. The MOA is unclear. It is unclear whether the drug will also protect cancer cells. • It is unclear what the compound is supposed to protect; the mechanism is not clear. • The experiments in milestone 6 need to be completed in order to demonstrate the rationale for this approach. • The application would benefit from toxicology input. • The mouse model is not the best choice and the design of the proposed studies need more focus.
GWG Votes	**Is the proposal feasible?**
Yes: 2	*none*
No: 11	• The application needs work. It is unclear whether this project is feasible and worth the effort. • The program is over ambitious and lacks the appropriate level of preclinical studies for a small molecule.

Application #	TRAN1-11313
Title (as written by the applicant)	Therapeutic development of human preterm umbilical cord derived mesenchymal stem cell conditioned medium for neonatal chronic lung disease
Translational Candidate (as written by the applicant)	Human preterm umbilical cord tissue-derived mesenchymal stem cell conditioned medium
Area of Impact (as written by the applicant)	Treatment of neonatal chronic lung disease, also known as bronchopulmonary dysplasia (BPD)
Mechanism of Action (as written by the applicant)	The product manufactured via culture of human preterm umbilical cord derived mesenchymal stem cells in serum free media is enriched with cell-secreted peptides (as seen via an advanced proteomics analysis) which are involved in immunomodulation, alveologenesis, and angiogenesis. This paracrine effect has been confirmed in an in vitro and an in vivo BPD model where the product provided injury protection and reversal when compared with inactivated heat treated product.
Unmet Medical Need (as written by the applicant)	BPD is a chronic debilitating disease of premature infants with high morbidity and mortality. Currently, there is no effective treatment to prevent or modify progression of BPD. Our study will develop the product as a therapeutic candidate for BPD.
Project Objective (as written by the applicant)	Pre-IND meeting and readiness for clinical trial.
Major Proposed Activities (as written by the applicant)	• Chemistry, manufacture, and control of the product in a GMP facility • In vitro and in vivo pharmacology to study the product in murine BPD • Regulatory and clinical strategy including FDA interactions
Statement of Benefit to California (as written by the applicant)	BPD is a chronic debilitating disease of premature infants with high morbidity and mortality. Preterm delivery rate in California is about 12% of all deliveries and approximately 50-80% of extremely preterm infants develop BPD. BPD is the second most expensive childhood disease after asthma, with a cost of about $2.4 billion annually. Currently, there is no effective treatment to prevent or modify progression of BPD. Our study will develop this product as a therapeutic candidate for BPD.
Funds Requested	$3,740,602
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	13
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. 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: 10	• Bronchopulmonary dysplasia (BPD) is a serious condition affecting premature infants but with long-term consequences. There are no effective treatments currently available thus there is a clear unmet medical need. • Bronchopulmonary dysplasia (BPD) is a chronic debilitating disease of premature infants with high mortality. These factors lead to a pathological development of the lung and pulmonary vessels, developing secondary Pulmonary Hypertension (PH). Certainly this clinical indication is devastating and serves as a clinical unmet need. There is a clear need and if successful, the impact would be significant.
No: 3	• There is a potential for impact but there are too many flaws in the limited data presented to be confident that this is a viable therapeutic candidate. • There is a need for additional basic science data on the mechanisms by which this potential approach is working. Such data will allow for a more robust regulatory discussion. • The product needs better definition.
GWG Votes	**Is the rationale sound?**
Yes: 3	• The approach could be sound if the mechanism of the potential product is better understood. • The proposal is missing data that would support a hypothetical MOA. • Very encouraging preliminary data has been presented; however, the animal model data would have been strengthened by presenting additional physiological data. • Additional basic studies should be performed to confirm (or dismiss) the 3 to 4 potential protein targets that are thought to contribute to the primary MOA.
No: 10	• The biology of BPD is complex including interruption of normal developmental signaling and inflammation. The rationale of this proposal is essentially that MSCs and their paracrine effect have been shown to have an immunomodulatory effect in other disease so perhaps will work for BPD. • The applicant has turned to preterm umbilical cords as a source for MSCs – the scientific rationale for why preterm cells would be better is unclear. Conditioned media (CM) from preterm umbilical cord MSCs seems to attenuate BPD injury. This is overall an imprecise approach that does not add much to our understanding of the disease or determining whether the therapy is effective, and by what means. • The CM is not characterized and it will be helpful to do so, in terms of what the FDA would like to see. It is unclear why the pre-term cells are better than cells from term cords. If this is better defined then the product may be easier to sell. At some point potency assays will need to be developed, so at least a hint of MOA would be helpful. • Using a hyperoxia model of BPD in mice, the administration of MSCs or conditioned media (CM) from MSCs provided some protection against the lung injury. This data from publications from 2009 and 2012 is a strength. However, the MSCs from preterm umbilical cord stem cells are currently poorly characterized. It is unclear how heterogeneous these cells are and how important the gestational age is. A better characterization of these cells would strengthen the application. • The data using CM from pre-term cords is not published and lacks details, making it hard to analyze the importance of the data. • The lack of mechanism of action is a concern. More studies should assess the primary factor(s) or peptide(s) before 100 banks/products from umbilical cord are produced without the ability to validate the product.The proteomic data is helpful but given the relatively short list of proteins that are detected at higher levels in CM there are some straightforward experiments that could address which proteins are most effective. • There is concern about proceeding with a conditioned media product when it may be possible to identify specific factors responsible for the effects observed so far.

	• One of the major flaws is a failure to address the very different stages of lung development that exist in pre-term infants and in the rodents that they are studying. • Since alveolarizaton in mice is very different in than humans, timing of doses and frequency may play a very large role in how the therapy works. • The mouse model of BPD is likely mild. Actual pulmonary artery pressures in the treated mice are needed in addition to the echocardiography data. A number of things can change the Doppler data beyond what the therapy may be doing. The Fulton index data is good, but data for actual numbers rather than ratios is needed, as well as heart rates and other data about the animal model. • MSCs as a therapy in diseased lungs is likely safe and so CM is likely also safe.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 1	• The plan is reasonable. It will not add much to the knowledge above what is presented in the proposal. • Though the authors state that in vitro assays (epithelial injury and angiogenesis) to test efficacy of the GMP product will work and be used in their proposal, this data is not included.
No: 12	• There are major problems in the model used in respect to the stage of lung development that is being addressed. • There does not appear to be a sound way to determine whether different batches of MSCs can be considered as equivalent. • Defining the details of product production is needed. • Additional characterization of the conditioned media will be necessary to move into human clinical studies - this will also assist with evaluation of lot-to-lot (donor-to-donor) variability. • Characterization of CM will allow for the development of a specification used to evaluate and determine or qualify each lot of CM. • More effort/planning for a pre-pre-IND meeting is needed. • One concern is what is needed to move this forward. A pre-pre-IND meeting would provide valuable input in light of the fact that it is unclear what is producing the response in the studies. • Results from the planned pre-pre-IND meeting should be valuable in planning. Re-application based on meeting feedback is suggested. The applicants need to carefully rethink what should be addressed in the meeting.
GWG Votes	**Is the proposal feasible?**
Yes: 8	• In the context of the goals of a TRAN1 award and based on the preliminary data and published work from the investigator it is not clear that the therapeutic is sufficiently ready, thus the likelihood of success seems low at this point. • If efficacy and safety are demonstrated then the proposal should be feasible. However, the applicants must achieve repeatability and consistent results (lot-to-lot/donor-to-donor) to correlate pre-clinical efficacy and ultimately clinical outcome. • Feasibility will depend on results of a pre-pre-IND meeting. • Questions were raised if this was the right animal model. • The experiments outlined seem feasible within the time frame.
No: 5	• At this stage, the case for this being a therapeutic strategy is not convincingly demonstrated. • The experience of the PI is limited. • The timeline is not sufficiently aggressive.

Application #	TRAN4-11271
Title (as written by the applicant)	Development of tumor microenvironment specific platform for the multi-parametric spatial analysis of cancer tissues
Translational Candidate (as written by the applicant)	High-parameter spatial imaging platform for the analysis of the tumor microenvironment in tissues from patients treated from iPSC derived CAR-T cells
Area of Impact (as written by the applicant)	Imaging technology bottleneck associated with the inability to measure both high parameters and the spatial dimension within the same tissue specimen
Mechanism of Action (as written by the applicant)	This platform uses a library of barcodes and reporters to reveal the staining pattern of an antibody panel across multiple cycles. Antibodies are labeled with DNA-based barcodes and the staining of sets of antibodies is measured through corresponding dye-labeled reporter probes. The work outlined in this proposal involves validating antibody panels for the analysis of the tumor microenvironment to reveal the complex organization of cells contained within this space.
Unmet Medical Need (as written by the applicant)	Treatment of solid tumors with CAR-T cells is confounded by the immunosuppresive nature of the tumor microenvironment. The tool outlined here enables detection of the spatial relationship between dozens of markers, enabling a deeper mechanistic understanding of CAR-T cell infiltration into the tumor.
Project Objective (as written by the applicant)	Readiness for transfer to manufacturing
Major Proposed Activities (as written by the applicant)	• Validation of tumor microenvironment specific antibody panel for the identification of key cell types within tumor tissues • Development of data analysis modules to identify cellular niches and characterize the overall immune state of tumor tissues • Design and test a microscope stage insert for high-throughput data acquisition on the fluidics instrument
Statement of Benefit to California (as written by the applicant)	CAR-T cell therapies provide great promise, but require additional investigation to treat solid tumors. By enabling clinicians to map the cell types within the tumor microenvironment, there is potential to discover key features of the mechanism of action, and with it, the design of more effective combination therapies. These enhancements could lead to widespread use of stem cell derived CAR-T cells and with it economic development and superior treatment options to the state of California.
Funds Requested	$1,044,683
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	13

(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	13

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. 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	• There is a genuine need for better analytical tools to study the modulation of the immune system in tumors. • There is scientific evidence in literature supporting that TME may play an important role in the success of adoptive cell therapy. Identifying TME parameters that make such therapies ineffective and targeting them can accelerate success for therapies. • Characterizing the immunosuppresive microenvironment of oncogenic tissue would have significant impact. • This is an innovative approach with the potential to lower the cost of treatment in a competitive field.
No: 7	• There is not an immediate clinical benefit, but over the longer term this tool might help to guide basic science research. • The technology is at a stage where it is too early to evaluate the impact of the tool. • In theory this tool could be helpful but it's not clear how using such a large number of antibodies will be superior to existing options.
GWG Votes	**Is the rationale sound?**
Yes: 3	• The rationale is sound but more thought should be put into the analytes measured. For example, it is unclear how the T cell therapy itself be detected (e.g. anti-CAR antibody), and whether the states of cells (e.g. STAT3) can be measured, rather than CD-type markers. • The rationale is sound but more preliminary data is needed.
No: 10	• The reagent element/immunostaining spectrum seems too broad/non-specific for clinical application. • The preliminary data on tissues is extremely limited and is largely restricted to T and B cell distribution. Preliminary proof of concept showing clinical utility is needed. • The potential of the various antibodies to cross react, lack of specificity, and loss of signal and background on the serial tests is a concern. It appears to work with a few antibodies but it is unclear if it will with 50. • It is unclear how the antibodies will be chosen; the right 50 is critical for this tool to be useful.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 0	*none*
No: 13	• The instrument seems to have been well-developed. This is probably the least complex of the 3 components. The proposal demonstrates that the signal reported is specific to the respective barcode/reporter combination with minimal cross-reactivity. • The proposal does not capture the complexity of developing 30-50 markers for tissue staining in a multiplex setting. A validation plan is needed for demonstrating sensitivity, specificity, cross-reactivity and manufacturability of antibodies required for TME signature. The minimally required features for a clinically relevant TME structural signature need to be identified. • There needs to be a focus on the quality of the detection of analytes versus quantity of analytes. The use of each antibody needs to be justified. • A justification of which reagents are necessary is needed. • The development of a software algorithm with multiple stains with structural TME components is extremely complex. The proposal does not show a prototype signature that has clinical relevance. • Software development will be the key to making the tool user friendly. It is unclear whether it is really possible to analyze 50 antibodies and determine where they are in space.

	● More clinically relevant examples needed. ● Early regulatory input for clinical application is needed.
GWG Votes	**Is the proposal feasible?**
Yes: 1	● This project appears to be a multi-year process.
No: 12	● TME is highly complex, and the TME structural components that are important for improving immunotherapy/CAR-T are likely to be different in different cancer types, and molecular subtypes. It is highly likely that there is quite a bit of variability in these components within a specific tumor type. Hence, a technology that assesses TME structural components should focus on a particular tumor type and provide a practical application that demonstrates association between a particular TME signature and a therapy, and the ability to capture the variability within that tumor type. The proposal fails to show any data demonstrating the association between specific TME markers to response/non-response to therapy. ● The proposal to develop and validate the multiplex staining protocol in 2 years is quite ambitious. ● The proposal appears overly ambitious, in that more than one of the milestones could easily take multiple years to accomplish. ● The regents alone may take many years to develop, so the timeline is too short. ● Validation studies etc. are complex and are likely to require a much longer time than available. ● To fully qualify all the analyte detection and antibodies is extremely difficult at this level of multiplexing.