$5,795,584 GWG RECOMMENDED
$0 BOARD APPROVED

							Score Range		GWG Votes						
APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Resubmission	Previous CIRM Funding	Disease Indication or Applicability	Product Type	Approach
TRAN1-10258	Development of ROR1 CAR-T cells to target cancer stem cells in advanced malignancies	$5,795,584	Y	88	85	5	75	90	11	2	N	N	Cancer	Cell Therapy	Autologous T cells engineered to target CSC
TRAN1-10275	Human Embryonic Stem Cell-Derived Natural Killer Cells for Cancer Treatment	$4,803,463	N	75	76	8	60	85	3	10	Y	N			
TRAN1-10285	Pre-clinical development of a small molecule for the treatment of osteoarthritis	$2,673,523	N	78	74	16	25	90	3	11	N	Y			
TRAN1-10294	hESC-derived retina organoids for vision repair in degenerative retina diseases.	$4,592,797	N	72	70	10	50	85	2	12	Y	Y			
TRAN1-10260	Extracellular Vesicles (EVs) from Allogeneic Cardiosphere-Derived Cells (CDCs) to Treat Acute	$4,941,382	N	70	69	5	60	80	0	14	Y	N			
TRAN1-10288	Cell-based therapy for Sepsis Induced ARDS	$3,392,303	N	65	66	6	60	75	0	12	N	N			
TRAN1-10330	Bioprinted Human Liver Tissue as a Therapy for Acute on Chronic Liver Failure	$3,719,531	N	60	62	3	55	65	0	12	N	N			
TRAN1-10282	Developing a therapeutic candidate for glioblastoma by targeting glioblastoma stem cells	$6,247,201	N	--	--	--	--	--	0	15	N	N			
TRAN1-10332	Novel combination therapy of repurposed FDA-approved drugs targeting liver cancer stem cells	$1,584,099	N	--	--	--	--	--	0	15	N	N			

Application #	TRAN1-10258
Title (as written by the applicant)	Development of ROR1 CAR-T cells to target cancer stem cells in advanced malignancies
Translational Candidate (as written by the applicant)	Autologous ROR1 CAR-T cell transduced with a lentiviral vector containing scFv (cirmtuzumab) with CD28, CD137, CD3zeta signaling domains
Area of Impact (as written by the applicant)	ROR1 expressing cancer stem cells in solid tumors and hematologic tumors
Mechanism of Action (as written by the applicant)	ROR1 CAR is a 3rd generation chimeric construct with an internal endodomain that transmits a CD3 zeta signal with added co-stimulatory signaling domains 4-1BB and CD28. When the transduced ROR-1 CAR-T cell comes into contact with its cognate receptor, a signal is transmitted by the CD3 zeta-chain, inducing lymphocyte proliferation and expression of trans-acting interleukins and chemokines that activate other immuno-reactive cells and in certain cases directly kill ROR1+ Cancer Stem Cells
Unmet Medical Need (as written by the applicant)	Compelling evidence suggests that dormant cancer stem cells (CSCs) are considered the origin of therapeutic resistance, and are responsible for relapse and metastasis. We will selectively identify and attack CSCs through the ROR1 receptor, using CAR-T cells to address this unmet medical need.
Project Objective (as written by the applicant)	Completion of a Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Generate GMP-compatible ROR1 lentivirus with a single-chain variable fragment (scFv) with three signaling domains derived from CD3zeta, CD28 and 4-1BB • Generate ROR1 CAR-T cells; complete studies of cell fate, persistence, efficacy and distribution in CLL, HNSCC, TNBC, ovarian, and pancreatic cancer • Develop a ROR1 Companion Diagnostic test
Statement of Benefit to California (as written by the applicant)	Californians will benefit from this project in several significant ways. If the therapeutic is successful, it will extend the long-term survival rates for Californians with solid and hematologic tumors. Accomplishing the proposed studies will have an added economic benefit for California through creating and maintaining skilled jobs, and using resources from in-state companies. High cost hospital stays and treatments associated with advanced disease, will be significantly reduced.
Funds Requested	$5,795,584
GWG Recommendation	***Exceptional merit and warrants funding, if funds are available***

Scoring Data

Final Score: 88

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

Mean	85
Median	88
Standard Deviation	5
Highest	90
Lowest	75
Count	13
(85-100): Exceptional merit and warrants funding, if funds are available	11
(1-84): Not recommended for funding	2

Score Influences
Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	11	1	1
Is the rationale sound?	11	2	0
Is the proposal well planned and designed?	8	2	3
Is the proposal feasible?	6	2	5

Reviewer Comments
The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths
- Solid tumor therapies would have significant impact.
- This is a novel immunotherapy approach for solid tumors.
- This is a well-written proposal with a reasonably identified contingency plan.
- The option/utility of being able to target multiple tumor types is intriguing and may contribute to the longer-term success of this approach as an optimal therapy to a particular tumor type.
- This is a study that needs to be done even though there are likely to be obstacles related to defense mechanisms of solid tumors. It should, at the very least, provide valuable insight into these mechanisms.

Concerns
- The relevance to cancer stem cells is unclear.
- Data that ROR1 targets cancer stem cells is limited.
- It is not clear what the role of ROR1 is in solid tumors.
- Potential concern is that the companion diagnostic assay(s) may not be necessary or useful.
- It would be useful to determine the biological role of ROR1 to determine the likelihood of the antigen loss.
- One way that cells escape CD19 CAR-T cell targeting is to down-regulate expression. If ROR1 is not necessary for viability, growth or proliferation then this approach may not be successful for the same reason as the CD19 CAR-T strategy.
- The studies of CAR-T cells in hematopoietic malignancies have shown a high relapse rate and this raises some doubt on efficacy of the overall approach.

Application #	TRAN1-10275
Title (as written by the applicant)	Human Embryonic Stem Cell-Derived Natural Killer Cells for Cancer Treatment
Translational Candidate (as written by the applicant)	Human embryonic stem cell (hESC)-derived natural killer (NK) cells to target relapsed/refractory Acute Myelogenous Leukemia (AML)
Area of Impact (as written by the applicant)	hESC-derived NK cells provide a novel and potent approach to treat relapsed or refractory AML that is resistant to current chemotherapy options.
Mechanism of Action (as written by the applicant)	hESC-derived NK cells provide a standardized, homogeneous, off-the-shelf cellular immunotherapy product that will be used as an allogeneic adoptive transfer treatment for patients with AML who have either never achieved remission with standard induction therapy, or who relapse after previous chemotherapy. hESC-derived NK cells kill tumor cells by several mechanisms: direct cytotoxicity, antibody-dependent cell-mediated cytotoxicity, induction of apoptosis and production of cytokines.
Unmet Medical Need (as written by the applicant)	Over 10,000 in the US die each year from AML, with 5 year survival <30%. Allogeneic NK cells are known to destroy AML cells in patients who have failed chemotherapy. hESC-derived NK cells will provide the first standardized, "off-the-shelf" cellular immunotherapy to treat this deadly disease.
Project Objective (as written by the applicant)	The objective is to have an FDA Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• We will use the GMP hESC line ESI-017 to produce a Master Cell Bank and Working Cell Bank of NK cells using defined clinical-scale cell methods. • We will demonstrate ESI-017 hESC-derived NK cells kill AML tumor cells 1) in vitro, and 2) in vivo using NSG mouse xenograft models. • We will assess safety of ESI-017 hESC-derived NK cells using an NSG immunodeficient mouse model to test tumorigenicity.
Statement of Benefit to California (as written by the applicant)	Over a thousand Californians are diagnosed with Acute Myeloid Leukemia (AML) each year, and five year survival in California is less than 30%. New treatment options are desperately needed for patients who fail standard chemotherapy. We will produce a standardized, off-the-shelf immunotherapy cell product that can induce remissions and lead to cure of AML. These studies with hESC-derived NK cells will allow Californians to be at the forefront of this cellular immunotherapy approach to treat AML.
Funds Requested	$4,803,463
GWG Recommendation	***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 average of the individual member scores. Additional parameters related to the score are shown below.

Mean	76
Median	75
Standard Deviation	8
Highest	85
Lowest	60
Count	13

(85-100): Exceptional merit and warrants funding, if funds are available	3
(1-84): Not recommended for funding	10

Score Influences
Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	12	0	1
Is the rationale sound?	4	5	4
Is the proposal well planned and designed?	0	10	3
Is the proposal feasible?	5	3	5

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- This is a novel idea that addresses a pressing medical need.
- The idea is an exciting concept.
- A uniform off-the-shelf cellular product is very much an attractive approach.
- The applicant received generally positive responses at a pre-pre-IND meeting.
- FDA response to a pre-pre-IND meeting is encouraging with no real concerns or issues.

Concerns

- The application needs to be revised to better address off-target effects and potential residual hESC safety concerns.
- Risks potentially outweigh benefits of this NK therapeutic approach (e.g. tumorogenicity, off-target effects and complete MHC mismatch).
- Better strategies to improve the detection of ES cells are needed to consider score in the fundable range.
- The pre-pre-IND meeting with the FDA seemed positive. However, the correct questions regarding testing for off-target killing were not raised.
- Multiple reviewers noted that off-target effects on hematopoietic cells and other tissues are not adequately addressed.
- Experiments to address potential off-target effects are considered to be critical for moving forward. The safety concern of off-target effects may be reasonably addressed with additional preclinical studies in the proposal.
- Cancer specificity experiments should be performed.

Additional Comments

- It is not clear whether the proposal intends to ultimately use the MCB prepared in this project to generate the cells that will ultimately be used in a clinical tral. If so, this bank may require more extensive testing than is indicated.
- The contingency plan should account for manufacturing risks. For example, it's unclear what happens if one parent hESC line is not stable during MCB/WCB generation, or if GMP compliant NK-differentiation does not proceed as efficiently at clinical scale as current preliminary research efforts.

Application #	TRAN1-10285
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, 423F
Area of Impact (as written by the applicant)	423F will be targeted to prevent the advancement of, or reverse, osteoarthritis
Mechanism of Action (as written by the applicant)	423F activates a patient's own cartilage stem/progenitor cells, helping them to repair cartilage damage. It also makes these cells more resistant to degenerative signals, thus interrupting the disease cycle. 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. 423F could become the new standard of care by slowing or reversing 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 determine dosage amount and formulation • Toxicity studies in rodents to verify safety of the drug • Testing dosage of 423F in a large animal model of OA and verifying that it is not toxic
Statement of Benefit to California (as written by the applicant)	5.9 million Californians suffer from some form of arthritis. Currently, treatments for osteoarthritis focus on pain management, only treating the symptoms of the disease. 423F activates cartilage stem/progenitor cells, making them resistant to degenerative signals and helping them repair cartilage damage. Therefore, 423F will 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	$2,673,523
GWG Recommendation	***Not recommended for funding***

Scoring Data

Final Score: 78

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

Mean	74
Median	78
Standard Deviation	16
Highest	90
Lowest	25
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	3
(1-84): Not recommended for funding	11

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	12	1	1
Is the rationale sound?	5	7	2
Is the proposal well planned and designed?	1	9	4
Is the proposal feasible?	4	3	7

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- *None noted*

Concerns

- This proposal should be revised to address concerns regarding animal study design. Tumorigenicity and off-target effects should be addressed earlier in the program, given the risks associated with the activated pathway.
- The group needs to have a more solid plan to address potential tumorigenicity generated with 423F before embarking on *in vivo* studies.
- Tumorigenicity should be more closely evaluated and likely performed in the earlier stages of this project.
- The group needs to define the use (or not) of microspheres before starting further experiments, as the use of such a delivery method dramatically changes the approach to study other features of the small molecule (e.g. bioavailability, biodistribution, etc).
- Potential negative off-target effects may require more attention.
- The application needs a better plan to address potential for off-target reactivity.
- Given the concerns, it is unclear whether the currently proposed molecule is considered a "lead candidate" for further development.
- The project tasks include a pre-preIND meeting but is not possible/available for a small molecule drug product.
- The team lacks expertise in formulation development.
- The team lacks expertise in tumorigenicity studies.
- One cannot exclude patients from a clinical trial who may have cancer histories before tumorigenicity results are available; the results are required before the clinical trial.

Additional comments

- There is a significant chance that the microparticle delivery system would actually be the best way to go.
- Team should acquire more expertise for regulatory activities (i.e. tumorigenicity and formulation) and develop an appropriate sequence of studies prior to enrolling large animals into the study.
- (From discussion & critique) This approach relies on surface chrondocytes. These cells may be long gone by the time the therapy is applied in the target patient population. Thus, there is some uncertainty about the presence and quantitative size of the necessary cell population that would potentially be responsive to the therapeutic compound.

Application #	TRAN1-10294
Title (as written by the applicant)	hESC-derived retina organoids for vision repair in degenerative retina diseases.
Translational Candidate (as written by the applicant)	Human stem cell (hESC)-derived retina organoids, manufactured under GMP conditions.
Area of Impact (as written by the applicant)	Retinal diseases with photoreceptors loss, such as retinitis pigmentosa, age-related macular degeneration, Stargardt disease.
Mechanism of Action (as written by the applicant)	Mechanism of action is based on cell replacement. Transplanted hESC-derived retinal progenitor sheets will mature 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. Therapies in current clinical trials only target trophic effects.
Unmet Medical Need (as written by the applicant)	This therapy targets retinal degeneration of photoreceptors and dysfunctional RPE, accompanied by vision loss, as seen in advanced stages of diseases such as Retinitis Pigmentosa (RP) and dry Age-related Macular Degeneration (AMD). Current clinical trials only target earlier disease stages.
Project Objective (as written by the applicant)	Pre-pivotal efficacy and GMP implementation.
Major Proposed Activities (as written by the applicant)	• Establish a working cell bank; retina organoid product characterization; GMP manufacture implementation. • Scale up manufacturing of retinal organoids under implemented GMP, validate transport and stability of the final product. • Preparation for preclinical studies; pre-pivotal efficacy study in 4 different immunodeficient and immunocompetent animal models.
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 both AMD and RP, for which no other therapy exists. An effective treatment will keep afflicted individuals productive, enhance State tax revenues and defray the health care cost burden to taxpayers. It will also lead to robust industry developments, effectively leading to job creation and tax benefits.
Funds Requested	$4,592,797
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 72

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

Mean	70
Median	72
Standard Deviation	10
Highest	85
Lowest	50
Count	14

(85-100): Exceptional merit and warrants funding, if funds are available	2
(1-84): Not recommended for funding	12

Score Influences
Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	8	5	1
Is the rationale sound?	2	10	2
Is the proposal well planned and designed?	1	10	3
Is the proposal feasible?	1	8	5

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- There is definitely a need to develop photoreceptor therapies to address a wide range of blinding diseases.
- Retinal degeneration is an important unmet medical need.
- The approach may be applicable to multiple important eye diseases.
- Despite remaining questions about some of the proof-of-concept data, applicant has generally been responsive to prior critiques and it seems time to go forward.

Concerns

- Data on transplants in RCS rats is still not convincing. In fact, the data appears to indicate that any early benefit provided by the transplant was lost at later time points.
- Proof-of-concept studies seem incomplete/not supportive of the rationale.
- Use of hESCs rather than iPSC should be re-thought. A lot of immunogenicity problems would be avoided using iPSCs when work is translated into humans.
- More preliminary data should be obtained on off-target consequences of mixed cell transplants.
- After making a good case for including RPE in transplants it was a surprise to see them now being removed.
- The premise rests on providing the complete construct but transplant of RPE is not addressed.
- The key rationale for the proposal is based on transplantation of fetal cell sheets. It has now been clarified that no RPE is included in the transplanted constructs. However, it is proposed that this therapeutic would be used to treat RPE-related diseases (e.g., AMD). So, without RPE, there is a disconnect with the rationale and disease selection.
- The HLA matching strategy is particularly troubling. The proposal includes recruiting patients that are an HLA match with the cell line. That will likely result in the inability to recruit sufficient patients for the clinical trial in the future.
- There were no details provided on the outcome of the pre-preIND meeting.
- CMC process is not well defined.

Additional Comments

- PreIND meeting is recommended prior to initiation GMP manufacture.
- The manufacturing process has a key risk that should be addressed early. The manual removal of the RPE and dissection of the photoreceptor sheet will pose a significant risk for aseptic processing. Media simulation trials should be conducted to insure that this is performed under aseptic conditions for both animal studies and future clinical production. Special equipment of improved cleanroom classification may be required.
- Applicant did not address concerns about transplanting and aligning the constructs in the retina.

Application #	TRAN1-10260
Title (as written by the applicant)	Extracellular Vesicles (EVs) from Allogeneic Cardiosphere-Derived Cells (CDCs) to Treat Acute Ischemic Stroke
Translational Candidate (as written by the applicant)	Extracellular Vesicles (EVs) from Allogeneic Cardiosphere-Derived Cells (CDCs) To Treat Acute Ischemic Stroke
Area of Impact (as written by the applicant)	A novel method to treat stroke to be used in combination with reperfusion therapy, thrombolysis and/or endovascular procedures.
Mechanism of Action (as written by the applicant)	This program offers a realistic adjuvant therapeutic option for stroke victims. We will advance CDC-EVs to an IND level for testing in a select population of stroke patients receiving current standard of care rt-PA therapy. EVs are an excellent therapeutic option for stroke because they have previously been shown to have anti-inflammatory properties, reduce apoptosis and offer the possibility of regenerative process induced by growth factors or the recruitment of endogenous stem cells.
Unmet Medical Need (as written by the applicant)	Stroke is currently treated using thrombolysis with recombinant tissue plasminogen activator (rt-PA or tPA) or endovascular procedures. However, only 13.5-31% of patients undergoing the procedures end up “normal” neurologically after reperfusion therapy. There is a need for a cytoprotective therapy.
Project Objective (as written by the applicant)	We will file a pre-IND application
Major Proposed Activities (as written by the applicant)	• Evaluate CDC-EVs bioactivity in an embolic stroke model alone and in combination with standard-of-care therapy, tPA • Establish CDC-EVs bioactivity in aged rodents and conduct gender analysis studies • Evaluate CDC-EVs bioactivity and safety in a large animal stroke model: mRI and behavioral analysis
Statement of Benefit to California (as written by the applicant)	Reperfusion therapies have been shown to be effective in up to 31% of patients who become clinically normal following either monotherapy of combined therapy. Neither thrombolysis nor endovascular procedures promote cytoprotection to prevent brain cell death associated with ischemic insults, nor do they promote brain neuroplasticity or regeneration. With CDC-EVs to treat ischemic stroke, we have the opportunity to have a tremendous impact on a large stroke patient population in California.
Funds Requested	$4,941,382
GWG Recommendation	***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 average of the individual member scores. Additional parameters related to the score are shown below.

Mean	69
Median	70
Standard Deviation	5
Highest	80
Lowest	60
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

Score Influences
Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	7	2	5
Is the rationale sound?	2	11	1
Is the proposal well planned and designed?	0	11	3
Is the proposal feasible?	1	7	6

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- There is a clear need for new therapies that extend quality of life and restore function after stroke.
- The incorporation of standard of care is a necessity and well addressed in this proposal.

Concerns

- Overall, the proposal is an ambitious list of experiments that are designed to determine whether EVs are a useful approach rather than a translational study that leads to an IND.
- There are still concerns about efficacy. The MOA is unclear and the components of the vesicle that have an effect should be narrowed down.
- Preliminary data have gaps: no histology with localization of the dye, quantal curves are ambiguous.
- The use of EVs is potentially interesting but the authors do not clearly define how the EVs are standardized and whether the ultra-purification approach outlined in the proposal lends itself to high-throughput production.
- The efficacy is still not clear and the details of the behavioral analysis are confusing and seem highly variable.
- The application does not show significant improvement over the previous version, which was reviewed quite negatively, especially with respect to absence of compelling evidence for efficacy.
- Some of the issues were addressed from the prior review. However, the data analysis still did not demonstrate proof-of-concept.
- A go/no-go discussion is lacking and the rationale for what the many different animal and injury models combined with different readouts are supposed to show to move forward with the program remains elusive.
- The studies have multiple behavioral read-outs without clear go/no-go criteria on the outcome measures.
- This reviewer had concerns on batch-to-batch purity.
- CMC is complete but there are concerns about scalability and consistency between batches.
- A significant concern is that centrifugal ultrafiltration is used for concentrating the EVs but this is not a scalable process. The team should be using a scalable process such as tangential flow filtration. Changes in

the downstream purification at a later date to accommodate the need to increase scale could result in significant changes in EV quality.

- It is unclear if dosing is performed based on protein concentration or concentration of some other key component. The key issue with using protein concentration is that remaining cell culture media components that are not part of the EVs could result in incorrect concentration and inconsistency in dosing EVs. If total protein is used, a diafiltration step should be included to reduce media protein residuals and an assay should be added to monitor levels of a marker protein from the media.
- Manufacturing process is not well-defined. It is unclear how consistency between batches will be assured in scale up.

Additional Comments

- Reviewers strongly recommend engaging a biostatistician to assist in the data analysis and planning.

Application #	TRAN1-10288
Title (as written by the applicant)	Cell-based therapy for Sepsis Induced ARDS
Translational Candidate (as written by the applicant)	ORBCEL-C is an umbilical cord cell product that has well demonstrated properties to reduce lung tissue injury and enhance repair of the injured lung
Area of Impact (as written by the applicant)	Acute respiratory failure in critically ill patients with the acute respiratory distress syndrome, specifically sepsis induced acute lung injury
Mechanism of Action (as written by the applicant)	The ORBCEL-C product works by multiple favorable mechanisms including the release of paracrine factors that reduce deleterious inflammation, enhance healing of injured endothelial and epithelial cells in the lung, enhance killing of bacterial pathogens, and improve oxygenation by reducing the quantity of excess fluid (pulmonary edema) in the lung. These cells also transmit mitochondria and microvesicles that can further enhance tissue and cell repair and recovery from acute lung injury.
Unmet Medical Need (as written by the applicant)	Acute respiratory distress syndrome (ARDS) is an orphan disease that develops in approximately 200,000 adult and children annually in the US. There is no specific biologic or pharmacologic therapy for ARDS. Medical care is limited to supportive care with lung protective mechanical ventilation.
Project Objective (as written by the applicant)	Pre-IND meeting with FDA (CBER)
Major Proposed Activities (as written by the applicant)	• Transfer of technology to generate ORBCEL-C cells for use in pre-clinical studies of ARDS. • Testing ORBCEL-C for efficacy in pre-clinical models of sepsis-induced ARDS in both mice and in an ex vivo perfused human lung preparation. • Generation of GMP ORBCEL-C cell product and integrating the CMC and the pre-clinical data for a Pre-IND meeting with FDA.
Statement of Benefit to California (as written by the applicant)	ORBCEL-C has high promise to be an effective cell-based therapeutic to treat the acute respiratory failure in critically ill patients with ARDS. This new therapy would be transformative in providing a novel reatment for ARDS, with the likelihood that both morbidity and mortality would be reduced. Clinical studies to date indicate that cell-based therapy is very likely to be safe. ORBCEL-C is ideal also because of its more economical and logistically available source, umbilical cords.
Funds Requested	$3,392,303
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 65

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

Mean	66
Median	65
Standard Deviation	6
Highest	75
Lowest	60
Count	12
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	12

Score Influences
Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	3	7	2
Is the rationale sound?	3	7	2
Is the proposal well planned and designed?	1	9	2
Is the proposal feasible?	3	5	4

Reviewer Comments
The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths
- The team and PI are exceptionally experienced to conduct the proposed experiments.
- The experiments are clearly explained and likely doable given the team's track record and prior experience with these mouse and *ex vivo* human models.
- The current state of the field of using MSCs to treat ARDS is that the initial experiments in mouse models suggested an immunomodulatory role that led to decreased inflammation and mortality and that phase I clinical trials did not identify serious safety concerns.
- The positive track-record of the investigators in this space is very well recognized.
- This is a great team with much valuable experience in MSC treatments for ARDS. The well-established animal models and lung perfusion model will be very helpful.

Concerns
- The major question is whether these cells are efficacious in humans with ARDS, and this will be determined in an ongoing phase 2 clinical trial and in future phase 1/2 trials using ORBCEL-C. The results of the phase 2 clinical trial would better inform the value in funding this proposal.
- Relevance of study compared to ongoing phase 2 clinical trial is not clear.
- The planned phase 1/2 trial of ORBCEL-C in moderate to severe ARDS would be more informative than the experiments proposed here.
- The success of technology transfer is essential for this technology to be beneficial here in the US; since a current clinical study is underway in Europe.
- The ORBCEL-C product should be evaluated head-to-head with BM-MSC in a more appropriate way to compare and demonstrate superiority of this new technology.
- Head-to-head comparison between bone marrow derived MSC and proposed product are required to give more clarity regarding *ex vivo* and *in vivo* function.
- The applicant needs to compare cord blood MSC derived by standard versus CD362-enriched methods.
- Few details were provided on tech transfer including the QC methods to be established. The team should strongly consider completing tech transfer and manufacturing cells at the collaborating institution for the proposed non-clinical studies.
- The HF bioreactor has very limited scale-up capabilities and would be limited to scale-out given that only one dose can be produced in each bioreactor run.
- More details should be provided on the cell separation. The details provided on the mAb that will be used for cell separation are insufficient and it is unknown whether the mAb meets the PTC guidelines for Abs used in manufacturing processes.

Additional Comments
- Preclinical studies are more powerful in the eyes of FDA when "clinical-grade"/cGMP cellular product is used to demonstrate early safety.

Application #	TRAN1-10330
Title (as written by the applicant)	Bioprinted Human Liver Tissue as a Therapy for Acute on Chronic Liver Failure
Translational Candidate (as written by the applicant)	A bioprinted liver tissue comprised of iPS-hepatocytes with supporting hepatic stellate cells and liver endothelial cells.
Area of Impact (as written by the applicant)	Bridge-to-recovery or bridge-to-transplant for patients with acute on chronic liver failure.
Mechanism of Action (as written by the applicant)	The proposed candidate provides a healthy hepatic biomass that increases hepatic reserve. The implanted liver tissue functions similarly to the native liver, providing synthetic and metabolic function that is anticipated to extend the lives of patients with ACLF to get them to liver transplant or help them recover.
Unmet Medical Need (as written by the applicant)	While the incidence of ACLF has grown steadily and is predicted to continue doing so, there have been no definitive therapies developed to provide increased hepatic function outside liver transplantation. This therapy will bridge patients to transplant and may eventually be definitive curative care.
Project Objective (as written by the applicant)	Pre-IND meeting with FDA
Major Proposed Activities (as written by the applicant)	• Product Development • Process Development
Statement of Benefit to California (as written by the applicant)	California, like other states, continues to see an increase in hospitalizations for cirrhosis and ACLF. ACLF hospitalizations are approximately 4X as expensive as those for cirrhosis alone and the proposed therapy aims to reduce the incidence of recurrent ACLF. Reducing the number of hospitalizations and long-term treatment costs, while increasing the time to transplantation and quality of life for California citizens will have a major economic impact on the state of CA and its citizens.
Funds Requested	$3,719,531
GWG Recommendation	***(1-84): Not recommended for funding***

Scoring Data

Final Score: 60

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

Mean	62
Median	60
Standard Deviation	3
Highest	65
Lowest	55
Count	12
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	12

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	6	6	1
Is the rationale sound?	1	11	1
Is the proposal well planned and designed?	0	13	0
Is the proposal feasible?	0	9	4

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- Potentially exciting idea.

Concerns

- Overall, the project seems premature to achieve a useful pre-IND meeting in the necessary time frame.
- There are concerns about sourcing of multiple cell types, consistency of product, and risk of having multiple mismatched cell types in the graft.
- The issue of immune reactions to the product are not adequately addressed.
- Mixed immunogenicity from accessory cell sources is not considered or addressed.
- The potential for foreign body reaction to the patch and potential for alloimmunization due to cells are not considered or discussed.
- Likelihood of foreign body reaction to the graft has not been assessed well due to the use of an immune-deficient mouse model.
- Phenotype of iPS cell-derived hepatocytes is less differentiated than adult hepatocytes. Is it unclear if the cells mature and, if so, how long the maturation process takes.
- There are concerns whether the iPS-derived cells will mature rapidly enough to have efficacy in humans. The cells would need to be functional at implantation.
- Phenotype/functional comparisons between induced cells and primary fresh hepatocytes are not strong.
- Feasibility of scale-up is a concern as only a small mass has been accomplished in rodents to date; the proposal needs a larger animal model to demonstrate efficacy and feasibility of scale-up.
- Feasibility at acute or chronic time points is doubted.
- It is not clear if surgical implantation in a cirrhotic liver is feasible as sutures do not hold in this tissue.
- Functional studies of induced hepatocytes do not appear to be presented in standard fashion in accordance with the literature.
- Concerns about sufficient expertise dampen enthusiasm.
- The team lacks expertise in many components of the project.
- Experienced liver surgeon/transplant surgeon involvement is missing.
- Information about the source and function of the non-iPSC cell components is inadequate.
- Standardization of production of accessory cells in terms of number and ratio are not well-described.
- There are concerns about quality control.
- The potential risks of the treatment to the patient are not adequately considered.
- Discussion of cost for the potential treatment was not provided.

Additional Comments

- The implications for immune suppression that may be required for allogeneic graft are unclear.
- The study needs addition of a large animal model to demonstrate potential for scale up.
- The team needs to get input from a liver transplant surgeon to understand acceptable forms of treatment.
- Manufacturing and testing information should be provided for all cell types that will be used in the printed construct.
- Information on how quality control will be done on the final bioprinted patch should be provided.

Application #	TRAN1-10282
Title (as written by the applicant)	Developing a therapeutic candidate for glioblastoma by targeting glioblastoma stem cells
Translational Candidate (as written by the applicant)	Small RNA-expressing lentivirus, which has demonstrated robust efficacy for targeting tumor stem cells in a glioblastoma (GBM) xenograft mouse model.
Area of Impact (as written by the applicant)	This candidate has the potential to be developed into a therapy for GBM, the most deadly primary brain tumor that has no effective therapy.
Mechanism of Action (as written by the applicant)	The proposed candidate is intended to correct disease phenotype by targeting cancer stem cells. The small RNA-expressing lentivirus is designed to knock down the expression of a factor that is critical for cancer stem cell-initiated tumorigenesis. Because cancer stem cells are highly tumorigenic and resistant to current radiation and chemotherapies, our translational candidate has the potential to lead to a more effective therapy for GBM, by combining with the current standard of care for GBM.
Unmet Medical Need (as written by the applicant)	There is no effective therapy for GBM. The 5-year survival rate for GBM patients is less than 5%. The therapeutic candidate we propose to develop in this study has the potential to lead toward the development of a new therapy for GBM to prevent tumor recurrence and prolong the lives of GBM patients.
Project Objective (as written by the applicant)	Pre-IND meeting and readiness for manufacturing.
Major Proposed Activities (as written by the applicant)	• To determine dose and regimen in rodent studies. • To develop biomarkers for monitoring treatment response. • To perform pilot safety study.
Statement of Benefit to California (as written by the applicant)	California is estimated to have ~12% of all cases of GBM in the U.S. The five-year survival rate for GBM is lower than 5%. Besides the emotional and physical pain GBM inflicts on families, it produces a medical and fiscal burden in California larger than any other states. The proposed candidate represents great potential for both California patients and industry. It would also help to maintain California's leading position in clinical developments by creating safe and effective therapy.
Funds Requested	$6,247,201
GWG Recommendation	***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 average 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

Score Influences
Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	7	5	2
Is the rationale sound?	0	13	1
Is the proposal well planned and designed?	0	11	3
Is the proposal feasible?	0	10	4

Reviewer Comments
The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths
- *None noted*

Concerns
- Reviewers noted a lack of discussion on the exceptionally well-studied problem of spread of transplanted virus in brain tumors. This has been a real problem in previous studies, but this potential limitation is not addressed.
- Lack of penetrability of vectors in solid tumors is a fundamental flaw of the proposed approach.
- The concern regarding tissue penetration of the viral vector is a key issue that would need to be addressed.
- It is not clear whether the treatment of organoids with lentiviral constructs will have sufficient penetration to even provide meaningful insight.
- The key experiment, which is whether treatment of primary precursor cells from the CNS with TLXshRNA would increase the sensitivity to temozolomide, appears to be lacking.
- One of the suggested rationales for treatment is the possibility of achieving selective targeting of tumor cells, but the data provided is not sufficient to evaluate this selectivity.
- The applicants provided supporting preliminary data in Figure 2 that knockdown of TLX expression suppressed growth in a variety of tumor cell lines, but the information did not include such critical information as the number of cells plated or the growth conditions used.
- In Figure 3, the supporting preliminary data appeared to indicate that GSCs were not eliminated at all, although they may be decreased in number. For example, the data was presented as yield of spheres formed and showed a decrease in initiating cells, but such an outcome does not indicate elimination of tumor forming cells.
- The transplantation data shown in Figure 4 was interpreted to mean that GSCs had been effectively eliminated, but the applicants did not provide information on how many cells were transplanted or how long mice were maintained. This makes it impossible to interpret the data.
- Transplantation followed by treatment at two weeks post-transplant showed a less dramatic effect than treatment at one week. If a delay in just one week in initiation of treatment decreases the efficacy so much, this is a great concern.

Application #	TRAN1-10332
Title (as written by the applicant)	Novel combination therapy of repurposed FDA-approved drugs targeting liver cancer stem cells
Translational Candidate (as written by the applicant)	Biomarker-guided therapy with repurposed FDA-approved drugs Novel combination of repurposed FDA-approved drugs (Romidepsin + ATRA) will be studied.
Area of Impact (as written by the applicant)	Cure and safety/toxicity/pharmacodynamics studies for late-stage metastatic hepatocellular carcinoma, cholangiocarcinoma and hepatoblastoma
Mechanism of Action (as written by the applicant)	Three high-throughput screenings were performed to identify the best combination of repurposed FDA-approved drugs. All-trans retinoic acid (ATRA) selectively kill CSC, but do not damage normal hepatocytes. HDAC inhibitor Romidepsin suppressed stemness gene expression. Combination of ATRA with Romidepsin reduced non-coding RNA (mir22hg) and stemness gene (OCT4, SOX2, NANOG) expression and inhibited the tumor-seeding and self-renewal abilities of CSCs resulting in apoptosis in vitro and in vivo.
Unmet Medical Need (as written by the applicant)	Targeted cancer therapy is to eliminate all malignant cancer stem cells (CSCs) and/or circulating tumor cells (CTCs: a tiny fraction of blood cells, often fewer than one in a million) for the prevention of relapse and metastasis. Patient. CTC biomarker is used to predict therapy response.
Project Objective (as written by the applicant)	Pre-IND meeting and application for FDA approval
Major Proposed Activities (as written by the applicant)	• Determine clinical safety and effective doses for Romidepsin and ATRA combination treatment in preclinical mouse models (randomized PDX mice mice). • Circulating tumor cells (CTC) in patient blood will be used for RNA profiling analyses, followed by bioinformatic analyses to stratify HCC patients • Assess patient poopulation of responses to the drug combination and randomized biomarker-guided preclinical trials will be used for proof of principle
Statement of Benefit to California (as written by the applicant)	The number of Californians have liver cancer due to hepatitis C infection, alcoholic liver disease or cholestatic diseases. Because Hispanics have an increased risk of developing liver cancer (HCC) and alcoholic liver diseases, California, the state with the largest Hispanic population in the US, will be impacted by this epidemic. Thus, developing HCC therapy will not only benefit the Californians suffering by HCC, but may also help the state's medical system to respond to this future challenge.
Funds Requested	$1,584,099
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 average 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

Score Influences
Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	3	8	3
Is the rationale sound?	0	13	1
Is the proposal well planned and designed?	0	12	2
Is the proposal feasible?	1	11	2

Reviewer Comments

The Following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- *None Noted*

Concerns

- Preliminary data are based on mouse models and the "human models" that represent established cell lines. There is thus no solid evidence of relevance to human tumors.
- Data on real human tumors appears to be missing.
- Data was not presented to establish a clear link with cancer stem cells. The significance relative to the CIRM mission was not clearly established.
- The stem cell component does not appear to be consistent with the CIRM mission.
- Lack of robust data in the mouse model does not warrant the work with hundreds of tumors and brings into doubt the feasibility of the project.
- PDX mouse model proposed is time consuming and laborious- feasibility of accomplishing the study in 960 animals is questionable.
- The applicant's response to the previous review comments on first submission of the application is insufficient.
- Proposed validation of the 50 genes should have been completed and submitted as part of the rationale rather than being an aim in the proposal.

Additional Comments

- The proposed studies may not be required to initiate an early-stage human clinical trial given that these are approved drugs and the proposal would utilize approved doses in a class of patients that have failed other available treatments.
- The stemness panel in Figure 3 is supportive of biomarker development.