TOTAL BUDGET: TRAN 2017, CYCLE 1

TIER 1 $4,085,948

TIER 2 $14,747,922

Application Number	Title	Score	Mean	SD	Low	High	Budget	Recommended for Funding	Score 85-100	Score 1-84
TRAN4-09884	A Novel, Robust and Comprehensive Predictive Tool Using Human Disease-Specific Induced Pluripotent Stem Cells for Preclinical Drug Screening	90	92	3	90	95	$1,000,000	Y	13	0
TRAN1-09814	Injectable pro-regenerative scaffold for treating symptomatic peripheral artery disease	90	92	3	85	95	$3,085,948	Y	14	0
TRAN4-09820	Magnetic Particle Imaging for monitoring the lifetime localization, viability, and clearance of cell therapies deep in vivo	81	80	7	70	88	$1,501,955	N	6	8
TRAN1-09781	A Splicing Modulator Targeting Cancer Stem Cells in Acute Myeloid Leukemia	80	78	4	70	85	$2,780,595	N	1	14
TRAN1-09877	hESC-derived retina organoids for vision repair in degenerative retina diseases.	70	71	5	65	85	$4,612,930	N	1	14
TRAN4-09902	Verification of Biodistribution and Viability Readouts for MRI-based Cell Tracking Agents in a Relevant Preclincal Animal Model	65	67	8	80	50	$770,674	N	0	15
TRAN1-09855	Targeting NF-kB in glioblastoma: A therapeutic approach	--	--	--	--	--	$2,934,323	N	0	15
TRAN3-09805	Novel Device for CAR T Cell Delivery into Brain Tumors	--	--	--	--	--	$2,147,445	N	0	14

Application #	TRAN1-09781
Title (as written by the applicant)	A Splicing Modulator Targeting Cancer Stem Cells in Acute Myeloid Leukemia
Translational Candidate (as written by the applicant)	17S-FD-895 is a potent small molecule splicing modulator that inhibits aberrant splicing in CSCs that have deregulated SF3B1 expression.
Area of Impact (as written by the applicant)	Development of 17S-FD-895 could address a major bottleneck to reducing AML mortality by targeting splicing deregulated-CSCs that fuel disease relapse.
Mechanism of Action (as written by the applicant)	17S-FD-895 will positively impact patients with AML by providing a potent and selective CSC-targeted therapeutic strategy that could prevent relapse and improve overall survival. In addition, splice isoform biomarkers of CSC response to 17S-FD-895 have already been identified. Through targeted modulation of the RNA splicing machinery, we can alter and monitor the splicing response to 17S-FD-895, which provides a vital companion diagnostic for proof-of-concept studies in future clinical trials.
Unmet Medical Need (as written by the applicant)	Despite recent advances in molecular targeted and immunotherapeutic strategies, patients with AML have a 5 year life expectancy of only 26% due to high relapse rates fueled by CSCs. CSCs are uniquely sensitive to splicing modulation and can be selectively inhibited by 17S-FD-895.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Manufacture sufficient quantities of 17S-FD-895 to complete key pre-IND studies • Complete non-clinical safety studies, pre-clinical studies and biomarker testing as proof-of-concept for future clinical applications • Complete pre-IND studies and have a pre-IND meeting
Statement of Benefit to California (as written by the applicant)	For nearly 50 years, no therapies have significantly reduced relapse-related mortality in AML. Available pharmaceuticals and immune-based therapies are limited to the amelioration of symptoms and/or the treatment of dependent conditions, such as anemia, bleeding or infections. A selective cancer stem cell-targeted agent, 17S-FD-895, offers a novel therapeutic candidate for AML patients and those suffering from other recalcitrant cancers, providing hope for many of our fellow Californians.

Funds Requested	$2,780,595
GWG Recommendation	***Score 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 average of the individual member scores. Additional parameters related to the score are shown below.

Mean	78
Median	80
Standard Deviation	4
Highest	85
Lowest	70
Count	15
Score 85-100: Exceptional merit and warrants funding, if funds are available	1
Score 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?	10	1	4
Is the rationale sound?	6	5	4
Is the proposal well-planned and designed?	3	5	7
Is the proposal feasible?	6	1	8

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

- AML is a significant disease. Current standard of care results in very high relapse rates and very poor overall survival rates (26% at 5 years). Thus there is a pressing unmet medical need for developing better therapies that could obviate relapse rates.

- This proposal addresses an important unmet medical need in a disease where there are limited SOC options and high relapse rates.
- The applicants have discovered that splicing deregulation represents a unique CSC therapeutic vulnerability, and therefore developing drugs to target the spliceosome machinery is a unique, novel approach; one that can work both directly and in conjunction with existing therapies.
- The body of available data supports the efficacy of splicing modulators in general, and it appears that 17S-FD-895 is also effective in preclinical models of leukemia.
- The overall plan for preparation for IND submission seems reasonable.
- Preliminary data that exposure to the correct concentrations of 17S-FD-895 can reduce growth/eliminate AML CSC while having minimal impact on normal HSC is reasonable for this stage of development.
- The team has done a great job of demonstrating that spliceosome dysregulation occur in CSCs and that it can be targeted to reduce proliferation of CSCs.
- Detailed biomarker plans to study PK, PD, MOA and tracking splice variants are provided in the proposal.
- Q&A with regulatory body is planned.
- PI is well-recognized for investigations on defining CSC in AML, is already well-funded by CIRM, and the primary collaborator seems to have the appropriate experience in small molecule drug optimization.
- The team has an excellent mix of biology and chemistry expertise.

Concerns

- Toxicology experiments are not well-developed and endpoint of selecting candidate drug is not well-described.
- The proposal needs expert advice and possibly small toxicity study before resubmission.
- Expert input on potential toxicity should be included prior to a request for funding.
- Proposal needs to clarify how toxicology studies will be conducted.
- The current program lacks appropriate evaluation of 17S-FD-8952's safety and pharmaceutical properties.
- Toxicity: Drug targets normal SF3B1 spliceosome, not mutant version, and is viewed as having an irreversible inhibitor activity. That would could call into question whether interfering with normal splicing modulation in non-cancer cells could trigger abnormal responses in healthy HSC or other tissues. It is unclear what preliminary Q&A with FDA entailed but, at a minimum, need to better address toxicology aspects.
- As the authors note: “Because of key differences between human and mouse pre-mRNA splicing regulation, the developmental therapeutic efficacy of splicing modulation must be quantified in humanized LSC model systems.” Presumably, given the species differences, performing toxicology studies in rodents will not be very useful.
- The key question is regarding toxicology studies. Although this is not part of the scope of the current program, a plan to advance this area is important. Given that the murine spliceosome differs from human, a different animal model will be required to assess toxicity.
- Toxicity is an important concern. Toxicology should be studied in multiple animal models.
- The proposed studies would benefit from being performed at a qualified CRO, including pilot safety studies in the rat and a non-rodent species.
- The applicant needs to address impact on biology in non-rodent systems.
- It is unclear whether splicing modulation will simply slow AML growth, or if it could lead to a cure by destruction of AML CSC. The experimental data showing splicing modulation can negatively impact survival of bulk AML as compared with normal bone marrow is convincing. However, whether AML CSC are “uniquely vulnerable” within the bulk AML compartment is less compelling.
- It is unclear what proportion of AML patients have spliceosome mutations, and will the presence of such mutations impact (positively or negatively) treatment response. The proposal

only states “high prevalence of splicing defects in AML." At a minimum, there may be a need to screen AML patients to determine who should be treated.

- The proposal needs to indicate how potential spliceosome mutations in subset of AML patients might impact drug activity/interactions.
- A structurally similar molecule (E7107) that entered clinical trials resulted in off-target effects.
- Two separate Phase I clinical trials of E7107 revealed an unexpected and unexplained side effect of visual disturbances in 5% of subjects. Further efforts are needed to determine whether this was an on- or off-target effect of U2 snRNP inhibition *in vivo*.
- Given that this class of therapeutic is relatively new and that vision loss was seen in the clinic for a similar molecule, much more detailed pre-clinical toxicology studies need to be done to evaluate acute and chronic toxicology effects. Mouse toxicology studies may not translate to humans.
- Although the plan calls for some evaluation, the basic criteria for advancement of the compound into the clinic is not well defined in terms of ocular toxicity or metabolic stability.
- Concern about known toxicology of this class of molecules was not adequately addressed.
- Methods for developing a human formulation need to clarified.
- The team lacks experience in GMP manufacturing and scale-up of small molecules.
- The teams would benefit from an experienced drug metabolism scientist and toxicologist who has small molecule drug development experience.

Application #	TRAN1-09814
Title (as written by the applicant)	Injectable pro-regenerative scaffold for treating symptomatic peripheral artery disease
Translational Candidate (as written by the applicant)	Injectable biomaterial derived from the natural scaffolding of porcine muscle
Area of Impact (as written by the applicant)	Improving the quality of life of patients with symptomatic peripheral artery disease.
Mechanism of Action (as written by the applicant)	The proposed mechanism of action is through recruitment of blood vessels and recruitment and differentiation of muscle stem cells. The injected material forms a new porous and fibrous scaffold, which contains appropriate tissue specific cues to stimulate muscle regeneration.
Unmet Medical Need (as written by the applicant)	The prevalence of peripheral artery disease is high in adults and while there are currently some useful symptom improving therapies, there is an unmet need for new therapies for the numerous individuals where these approaches are not successful to improve blood flow and muscle function.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Manufacture product to support nonclinical studies required by FDA • Nonclinical safety studies • Clinical trial planning and development
Statement of Benefit to California (as written by the applicant)	The prevalence of peripheral artery disease is 12% and represents a population that is approximately equal to that of coronary artery disease. The significant reduction in quality of life and high healthcare cost burden necessitates the development of new therapies for these patients. Our injectable biomaterial is a cost effective regenerative medicine strategy to improve blood flow and muscle function, thereby improving patient quality of life.
Funds Requested	$3,085,948
GWG Recommendation	***Score 85-100: Exceptional merit and warrants funding, if funds are available***

Scoring Data

Final Score: 90

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

Mean	92
Median	90
Standard Deviation	3
Highest	95
Lowest	85
Count	14
Score 85-100: Exceptional merit and warrants funding, if funds are available	14
Score 1-84: Not recommended for funding	0

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?	10	0	4
Is the rationale sound?	13	0	1
Is the proposal well-planned and designed?	12	0	2
Is the proposal feasible?	13	0	1

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 unique product as it is designed to treat both ischemia and muscle dysfunction associated with peripheral artery disease (PAD).
- A strong overall plan is presented that can use their lead product in development as a scientific as well as a regulatory roadmap.
- If the therapy is deemed effective then the roadblocks to commercialization will be lower due to financial considerations, logistics/transport, and ease of requirements with extracellular matrix (ECM) compared to cellular therapy.
- Initial pre-clinical studies demonstrated significant results in end points of increased vascular perfusion and increased muscle development as well as safety and proof of concept.
- The applicant provided good responses to previous reviewer comments.

Concerns

- They have an appropriate statement of work required to move the technology to the IND application phase, but reviewers recommended having a pre-pre-IND meeting with the FDA to align the IND plan with the FDA medical review team. There is no guarantee that same reviews will be used on this product as those for their lead product in development.

- Some concern was expressed about whether peripheral artery disease is a highly significant unmet medical need. The inclusion of patients with critical limb ischemia as a potential target group mitigates that concern.
- It was recommended that the group involve patients with Critical Limb Ischemia (CLI) as soon as possible due to the significant impact that may bring to that large population of patients in which there's no other therapeutic alternative.
- The investigators should evaluate the possibility of including more severely affected CLI patients in the clinical trial population.

Application #	TRAN1-09855
Title (as written by the applicant)	Targeting NF-kB in glioblastoma: A therapeutic approach
Translational Candidate (as written by the applicant)	Our target is NF-kB transcription factors and the therapeutic molecule is NEMO-binding domain peptide which prevents the activity of NF-kB proteins
Area of Impact (as written by the applicant)	Glioblastoma multiforme (GBM), a deadly disease
Mechanism of Action (as written by the applicant)	Our target is NF-kB transcription factors and the therapeutic molecule (NEMO-binding domain peptide) prevents the activation of IkB complex (IKK) which is unable to phosphorylate IkB bound to p50-p65 NF-kB proteins. Because IkB is not degraded due to a lack of phosphorylation, the kB proteins are unable to translocate to the nucleus and unable to activate NF-kB inducible genes. A mutant NEMO binding peptide has no effect on NF-kB activity.
Unmet Medical Need (as written by the applicant)	Median survival is only 12 to 15 months for patients with glioblastomas. Almost all patients showed occurrence of the tumor. We have identified NF-kB activity in the glioma stem cells essential for tumorigenesis. Our inhibitor peptide prevents the ability of glioma cells to divide and proliferate.
Project Objective (as written by the applicant)	Have sufficient efficacy data for pre-IND meeting.
Major Proposed Activities (as written by the applicant)	• Synthesis of NBD peptide, route and dose of administration, and efficacy in mouse models. • Treatment with the NBD peptide of mice transplanted with human GBM cell lines and PDX-xenografts. • Determination of the efficacy of the treatment with the inhibitor in reducing the mass of the tumor and enhancing the lifespan.
Statement of Benefit to California (as written by the applicant)	GBM is a deadly disease and there are a number of major hospitals in California who take care of patients with this disease. The disease is invariably deadly and the survival is only approximately 12-15 months after detection of the tumor. Our inhibitory molecule can not only reduce the mass of the tumor, but also extend the life of the patient--things that are not possible with the current treatment of chemotherapy.
Funds Requested	$2,934,323

GWG Recommendation	***Score 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
Score 85-100: Exceptional merit and warrants funding, if funds are available	0
Score 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?	5	8	2
Is the rationale sound?	0	12	3
Is the proposal well-planned and designed?	0	12	3
Is the proposal feasible?	0	14	1

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

- NF-kB signaling appears to be an important feature of aggressive forms of glioblastoma multiforme.

Concerns

- Several key experiments are needed to help support the utility of the NBD peptide as a human therapeutic.

- There are over 4000 papers on NF-kB inhibitors in cancer over the last 25 years, and no discussion of why the proposed one would be any better.
- It is not clear if the applicant's candidate therapeutic is better than the other inhibitors that utilize a similar mechanistic foundation.
- Peptide based therapeutics are a feasible drug design approach. However, a potential issue is the ability of peptide therapeutics to adequately penetrate the blood-brain barrier and gain access to the parenchyma. At this point, it is unclear whether the NBD peptide has acceptable penetration characteristics.
- The size of the putative therapeutic(s) is reasonably large and would not necessarily be expected to cross the blood-brain barrier (BBB) in effective amounts. Proposed strategies all involve systemic delivery (although, direct delivery proposed if systemic toxicity occurs) that could be associated with sub-therapeutic distribution across the BBB.
- Peptide therapeutics can be readily metabolized by circulating endogenous proteases and peptidases thereby limiting the pharmacokinetic performance of the drug. At this point it is unclear whether the NBD peptide is stable in human blood.
- The standard in the field for GBM therapeutic development is using aggressive human GBM cells enriched for CSC activity. No convincing rationale is offered for the use of mouse models in this proposal.
- Rodent models of GBM often do not provide accurate surrogates for GBM therapeutic success. In fact, other therapeutics have shown complete eradication of malignant glioma in rodent models but have not seen success in clinical trials. This problem is not unique to this therapeutic or paradigm, though. Nevertheless, data from the proposed rodent studies could inform dosing and toxicity, as well as tumor biology.
- NF-kB signaling is probably used by every cell in the body, yet there is no discussion or examination of possible side effects.
- Cancer treatment is generally based on combinations of agents. There is no consideration of this in the proposal.
- The program plan, in general, will allow for a basic understanding of the pharmacology and efficacy of the NBD peptide. However, considerations related to the compound's safety and pharmacokinetic behavior need to be further refined for a pre-IND meeting with the FDA.
- In general, the pharmacology and efficacy portion of the program are well constructed. However, the evaluation of safety, pharmacokinetics, and metabolism of the NBD peptide should be further refined and expanded. Furthermore, the scientific approaches should also be carefully considered as the therapeutic is a peptide and not a small molecule drug.

Application #	TRAN1-09877
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)	Demonstration of efficacy, Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Establish a working cell bank; retina organoid product characterization; GLP manufacture implementation; demonstration of purity, stability. • Scale up manufacturing of retinalorganoids under implemented GLP, validate transport; test immunology in vitro. • Preparation for preclinical studies: (1) safety feasibility and (2) efficacy study in 3 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	$4,612,930
GWG Recommendation	***Score 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 average of the individual member scores. Additional parameters related to the score are shown below.

Mean	71
Median	70
Standard Deviation	5
Highest	85
Lowest	65
Count	15
Score 85-100: Exceptional merit and warrants funding, if funds are available	1
Score 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	6
Is the rationale sound?	3	5	7
Is the proposal well-planned and designed?	1	7	7
Is the proposal feasible?	3	4	8

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

- Multiple animal models were tested using a variety of assessments of transplant success (electrophysiology, anatomy, psychophysics).

- Matrigel was used as ECM for cells that were produced for the animal studies. In the proposed studies the team is moving away from Matrigel to a defined matrix. That is an important improvement.
- Focus on cell manufacturing for clinical studies is important to advance the program.

Concerns

- This project is too early in the development program to apply for this Translational award. The key is having POC data in animals with a single candidate. It's not clear that the team has this data since what was presented is very weak.
- A regulatory plan is not in place. This reviewer suggests engaging a regulatory consultant with experience in pre-preIND and preIND submissions.
- The results of the completed animal studies are not convincing.
- Additional preliminary data are needed to support POC.
- Results from POC studies demonstrated variable visual outcome at different times after transplant (e.g., 3 vs 4-5 months outcomes in Figure 5), evidence of host retinal atrophy over transplant (e.g., Figure 5, 8, 11 (at 209 days)) possibly involving inner retina, and incomplete assessment of recipients by ERG (missing 209 day time point).
- ERG data was not provided for the animals followed more than 3 months post-transplant. The data at 2 months transplant for ERG was very weak. The OKN data also was weak given the 3-month time point.
- The proposed studies fail to consider explicitly the immunogenicity of RPE developing in the organoid (vs. "motor grafts") and the possible long-term effects on immunogenicity of the organoid.
- Pilot tumorigenicity studies are not needed until final product "engineering run."
- More QC work is needed for off-target cells and to characterize the heterogeneous cell population that will be present in PRPs. The residual undifferentiated iPSCs should also be further studied since this is a key safety concern.
- Manufacturing on Matrigel may be an issue. It is not clear if switching from Matrigel to a defined matrix will alter the cell properties. It is also not clear if POC animal studies were done with Matrigel or the newer defined matrix.
- Studies should be conducted to determine that the change from Matrigel to a defined ECM does not have a significant negative impact on cell function.
- In the proposal it was stated that the trial would eventually enroll patients who have a favorable HLA match with the cell line to help minimize immune response. However, the undisclosed HLA type of the product may be rare and may present a problem for patient recruitment.

Application #	TRAN3-09805
Title (as written by the applicant)	Novel Device for CAR T Cell Delivery into Brain Tumors
Translational Candidate (as written by the applicant)	A novel surgical device that is capable of removing brain tumors, and allowing for direct injection of anti-cancer stem or immune cells into tumors.
Area of Impact (as written by the applicant)	Delivery of large number of cytotoxic anti-cancer stem cells or engineered immune cells into the brain is not possible with current technology.
Mechanism of Action (as written by the applicant)	The automated robotic Device is capable of detaching, fragmenting, cauterizing and aspirating brain tumor tissue through a small channel. The cavity generated in the tumor by the Device can then be used to dislodge large number of anti-cancer cytotoxic stem cells or engineered immune cells (T cells) directly into the residual tumor mass. This technology will allow for delivery of larger number of anti-cancer cells, which will improve the efficacy of these cell-based therapies for brain cancers.
Unmet Medical Need (as written by the applicant)	Even with standard multimodal therapies with surgery, chemo and radiation, most patients with malignant gliomas (glioblastoma) live less than two years after the initial diagnosis. This Device will have significant impact as it allows for direct delivery of cytotoxic biologic agents into tumors.
Project Objective (as written by the applicant)	Pre-IDE meeting
Major Proposed Activities (as written by the applicant)	• IDE Design Phase
Statement of Benefit to California (as written by the applicant)	We propose to develop a novel neurosurgical instrument that will allow for rapid and safe removal of brain tumor tissue using minimally invasive techniques. The cavity generated by the instrument can then be used for delivery of novel therapeutics directly into tumors. Successful development of this instrument will have a direct impact on public health by providing alternative therapies for malignant tumors.
Funds Requested	$2,147,445
GWG Recommendation	***Score 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	14
Score 85-100: Exceptional merit and warrants funding, if funds are available	0
Score 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?	2	9	3
Is the rationale sound?	0	12	2
Is the proposal well-planned and designed?	0	11	3
Is the proposal feasible?	2	10	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

- The proposal is from a PI who is also part of currently approved clinical trials of CAR T-cell therapy for recurrent GBM.

Concerns

- GBM is an insidious disease in which tumor cells emanate from a core and infiltrate the brain in irregular patterns. The goal of a neurosurgeon is to remove as much of the tumor as possible in a way that spares function to the greatest possible degree. In making decisions balancing tumor de-bulking with quality of life, the neurosurgeon will follow the tumor's irregular form as far as possible while sparing critical functions. Given this, it makes no sense to develop a device that would create a circular hole in the brain of defined size in which to put stem cells that may or may not extend survival.
- One of the critical aspects of neurosurgery is sparing necessary parts of the brain whenever possible. This blunt tool has no ability for such surgical finesse.
- This proposal does not address the unmet medical need.

- The rationale is not clear, as GBM cells are widely distributed throughout the brain. Thus, if proximity to tumor cells is required, then data on cell distribution is essential. If the proposal is to activate immunotherapy, then it is unclear why specific localization of transplanted cells would be necessary.
- This is a device looking for an application, and stem cell delivery for GBM is NOT the appropriate target.
- The value of the device is not clear, as a hole is already created during bulk resection and a catheter could be put in.
- It would be important to determine if this technology is better than other minimally-invasive port technologies, which have the advantage of direct visualization, non-orthogonal resection and similar size characteristics as those proposed by the applicants.
- Real-time imaging (or intermittent imaging during cavitation/tumor resection) would enhance understanding and assessment of complications and feasibility (in animal and human studies). Ultrasound (as proposed could be useful) but may not have the resolution/specificity of computed tomography scanning or magnetic resonance imaging.
- Dog animal models of naturally occurring malignant gliomas are not rare and would be best for assessing this technology. There are centers nationally (including California) that have access to these animals.
- Determining the effect of coagulation on therapeutic cell transport in the interstitial space will be critical. The therapeutic impact of regional cell based treatment for GBM needs to be better elucidated.
- Data for CAR-T cells as a therapeutic modality is not convincing (and a different CAR-T trial appears to have run into significant safety issues).
- CAR-T safety is a concern for this reviewer. For example, the JUNO conducted clinical trial is on hold due to death of patients from brain edema complications.
- The device is interesting but it appears that CAR-T cell therapy will not be effective for this indication.
- If the device malfunctions during surgery how will the device be retrieved? The device may not be optimal for large invasive GBM.

Application #	TRAN4-09820
Title (as written by the applicant)	Magnetic Particle Imaging for monitoring the lifetime localization, viability, and clearance of cell therapies deep *in vivo*.
Translational Candidate (as written by the applicant)	Pulsed-mode Magnetic Particle Imaging for monitoring the lifetime localization, viability, and clearance of cell therapies deep *in vivo*.
Area of Impact (as written by the applicant)	Cell therapy development bottleneck due to lack of in vivo monitoring which is quantitative, whole-body, longitudinal, determines graft viability.
Mechanism of Action (as written by the applicant)	Magnetic Particle Imaging directly images safe iron oxide tracers labeled to cell grafts and is clinically translatable. Pulsed MPI uses tracer magnetic relaxation signals to improve spatial resolution and measure local environmental variables such as intracellular viscosity and binding; leading to physiologic contrast that we can exploit to determine graft viability *in vivo*.
Unmet Medical Need (as written by the applicant)	We currently lack a cell tracking modality capable of robustly and quantitatively imaging cell therapies deep in the body at weeks- or months-long scales. An imaging method to monitor graft localization and viability could greatly expedite development and clinical adoption of cell-based therapies.
Project Objective (as written by the applicant)	Technology translation to commercial MPI scanners.
Major Proposed Activities (as written by the applicant)	• Translate Pulsed-MPI hardware and algorithms to 3D murine MPI scanner and test for 5-fold resolution and 20-fold SNR boost • Assess pMPI for cell viability detection using oligodendrocyte precursor cell model in vitro • Validation of MPI for monitoring OPC therapy success in a myelin-deficient shiverer mouse model
Statement of Benefit to California (as written by the applicant)	Stem cell therapy has enormous promise to become a viable therapy for a range of illnesses, including cardiovascular disease, diabetes, stroke, and Alzheimer's. If we could expedite the development of these therapies using a robust imaging method to monitor and validate candidate cell therapies, it would be of enormous benefit to both the patients of the State of California, as well as greatly reduce the medical costs for the State.
Funds Requested	$1,501,955
GWG Recommendation	***Score 1-84: Not recommended for funding***

Scoring Data

Final Score: 81

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	80
Median	81
Standard Deviation	7
Highest	88
Lowest	70
Count	14
Score 85-100: Exceptional merit and warrants funding, if funds are available	6
Score 1-84: Not recommended for funding	8

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?	10	3	1
Is the rationale sound?	4	7	3
Is the proposal well-planned and designed?	6	2	6
Is the proposal feasible?	8	2	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

- This is an excellent and timely application that has the potential to significantly improve existing imaging tools for *in vivo* quantitative and persistent cell tracking.
- A very good team is proposed.
- This represents cutting edge technology in an important area and should provide a valuable tool even in a first generation product.
- The proposal is based on a strong scientific and engineering rationale, well-prepared and supported by strong data, accompanied by an excellent engineering base and a motivated team to carry out the proposed activities.
- There is a considerable amount of preliminary results that supports the improvements in sensitivity and spatial resolution, and the development of a novel relaxation-contrast imaging

tool for non-invasive detection of cell viability. There are still some minor concerns associated with translating relaxation data from *in vitro* experiments to *in vivo* studies.

- The project has strong preliminary evidence of feasibility and proposed methods of improving sensitivity and resolution are supported by theory.
- Improvements in hardware design and image analysis in development of 3D pulsed MPI will likely improve signal sensitivity and spatial resolution.
- The investigators propose quantitative milestones that will move the product toward manufacturing.
- The OPC tracking application in Milestone 3 is appropriate for this technology and the investigators have demonstrated proof-of-concept tracking for months.

Concerns

- The proposal lacks clarity that this methodology reveals whether the cells that are delivered are alive or whether the nanoparticles are taken up by macrophages.
- While better resolution of the cells is a tremendous advance it still may not be able to detect the difference between live and dead cells and macrophages.
- The technology will still have problems tracking viable cells.
- The review discussion highlighted the issue of how to be sure label stays in the cells that were initially administered. The applicants need to address that concern more effectively.
- Better understanding (data) for distinguishing specific labelled cells vs non-specific uptake in macrophages (other cells) is needed.
- The proposal lacks the data to demonstrate which of the cells detected are those that are injected or endogenous cells engulfing the label.
- The issue of where the label goes when the labeled cell dies is still significant for implementation of this imaging technology. Studies with clear data demonstrating the fate of the label *in vivo* following cell death are critical.
- There are some concerns about Milestone 2 as to how the viscosity measurements will relate to cell viability. This study lacks validation and it is not clear that this feature will be ready for incorporation in the manufactured product, although it is good that the investigators realize a key challenge of this technology is the ability to probe cell viability.

Application #	TRAN4-09884
Title (as written by the applicant)	A Novel, Robust and Comprehensive Predictive Tool Using Human Disease-Specific Induced Pluripotent Stem Cells for Preclinical Drug Screening.
Translational Candidate (as written by the applicant)	A library of induced pluripotent stem cell-derived cardiomyocytes from healthy subjects as well as patients with common hereditary cardiac disorders.
Area of Impact (as written by the applicant)	Preclinical toxicity screening and drug discovery.
Mechanism of Action (as written by the applicant)	Patients with pre-existing cardiac conditions are more susceptible to drug-induced cardiotoxicity than general population. Including iPSCs derived from this subset of patients along with control iPSC-CMs in an *in vitro* assay will likely represent the heterogeneity of random population in a clinical trial and will help titrate the threshold for cardiotoxicity in high-risk patients.
Unmet Medical Need (as written by the applicant)	The current preclinical assays are suboptimal and lead to elimination of many potentially promising candidates . Use of this industry-standard patient-specific iPSC-CM library will help accelerate clinical trials by accurate prediction of proarrhythmic liability in high-risk population.
Project Objective (as written by the applicant)	Readiness for transfer to manufacturing.
Major Proposed Activities (as written by the applicant)	• Generation of iPSC-CMs from 40 patients with diverse genetic and disease background. • Detailed molecular and functional characterization of iPSC-CMs using immunofluorescence, patch clamp, calcium imaging, and other tools. • Validation of iPSC-CMs using a panel of high, intermediate, and low risk proarrhythmic drugs by high throughput multielectrode array (MEA).
Statement of Benefit to California (as written by the applicant)	California has many pharmaceutical and biotech companies. Currently, a major challenge faced by these companies is the increasing rate of drug withdrawal from market due to unpredictable cardiotoxicity, which is largely due to inefficient screening assays. The proposed predictive tool comprising of human iPSC-CMs from patients with diverse genetic background will revolutionize drug toxicity screening by accurately predicting

	cardiotoxicity in clinical trials and will reduce the overall cost.
Funds Requested	$1,000,000
GWG Recommendation	***Score 85-100: Exceptional merit and warrants funding, if funds are available***

Scoring Data

Final Score: 90

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

Mean	92
Median	90
Standard Deviation	3
Highest	95
Lowest	90
Count	13
Score 85-100: Exceptional merit and warrants funding, if funds are available	13
Score 1-84: Not recommended for funding	0

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	0	2
Is the rationale sound?	11	0	2
Is the proposal well-planned and designed?	9	0	4
Is the proposal feasible?	11	0	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

- There is a clear need for improved *in vitro* models to predict drug cardiotoxicity. The focus on iPSC technology to include genetic disease models is a strength.
- All necessary tools are in place and there is a clear plan to relate cell phenotypes to cardiotoxicity of a panel of drugs.

- Excellent validation of physiology and demonstration that test can detect drug side effects that are missed by current standard technologies.
- There is a comprehensive strategy for cell characterization, especially electrophysiology.
- The team is outstanding, containing leaders in stem cell technology, cardiology, pharmacology, translation, and regulation.
- Great stem cell science to address a significant need across the pharmaceutical industry carried out by a world class team.

Concerns

- The proposed plan does not adequately address challenges in manufacturing the product.
- Manufacturing and distribution of a stable, consistent product have not been sufficiently addressed.
- Focus on manufacturing and stability is important to the long-term success of the program.

Application #	TRAN4-09902
Title (as written by the applicant)	Verification of Biodistribution and Viability Readouts for MRI-based Magnelle® Cell Tracking Agents in a Porcine Model.
Translational Candidate (as written by the applicant)	This is a tool for tracking cell fate and viability *in vivo* post transplantation.
Area of Impact (as written by the applicant)	Bottlenecks include monitoring cell fate to aid patient stratification and prognosis for cardiovascular, neurological, and other conditions.
Mechanism of Action (as written by the applicant)	Magnelles are derived from the non-pathogenic bacteria that synthesizes lipid-enclosed magnetite particles, which are visible using T2 and T2* weighted magnetic resonance imaging (MRI). Magnelle labeled cells are visualized as regions of dark regions in MRI, distinguishing transplanted cells from surrounding tissue. We hypothesize the LCS feature is due to the bacterial origin of Magnelles and phagocytic cell types innate ability to clear them, in contrast to synthetic contrast agents.
Unmet Medical Need (as written by the applicant)	The inability to track the location and fate of transplanted cells non-invasively is slowing translation of cell therapies. Our proposals is to expand from small animal validations and show Magnelle-powering can provide these data in large animals.
Project Objective (as written by the applicant)	Confirm small animal results in large animal.
Major Proposed Activities (as written by the applicant)	• Validate Magnelle labeling of ~107 MSCs and confirm MRI expectations required for pig studies. • Surgery and injection of Magnelle labeled MSCs into pig spine. • Large animal study data collection and analysis.
Statement of Benefit to California (as written by the applicant)	Our company is located in CA and this work will directly support job growth both directly, and indirectly through our CA-based collaborations with other institutions. Many of the researchers interested in using our tool are based in CA. Other approaches are being pursued to meet the emerging regulatory requirements. However, based on the unique features of our tool, we are on pace to be this solution and become another example of a successful CA-based breakthrough.
Funds Requested	$770,674

GWG Recommendation	***Score 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	67
Median	65
Standard Deviation	8
Highest	80
Lowest	50
Count	15
Score 85-100: Exceptional merit and warrants funding, if funds are available	0
Score 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?	2	11	2
Is the rationale sound?	1	6	8
Is the proposal well-planned and designed?	2	5	8
Is the proposal feasible?	5	6	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 proposed product belongs to new class of magnetic imaging reporters, "Magnelles," that exhibit signal persistence up to 14 days (perhaps longer) that can be monitored by pre-clinical/clinical MRI and MPI techniques, and provide unique cell viability sensing capability, addressing unmet needs in stem cell therapies.
- The product (Magnelle cell tracking solution) is very likely to be successfully developed as a pre-clinical/clinical imaging tool (reporter) for validating biodistribution and viability for stem cell therapies and is an attractive value proposition. A strong rationale for proceeding with a porcine model is provided.

- The applicants have performed process improvement on the technology including increased magnetism for MRI, measurement to provide lower variability, confirmed antibody function and direct visualization of the Magnelles to validate expectations of the kit.

Concerns:

- The key for imaging of cell therapies is localization and assessment of viability of delivered cells. It is not clear to that this technique can sense whether a cell is alive or dead, or whether the marker is still confined to the delivered cell or has been taken up by a different host cell.
- A need for accurate cell tracking will be an important technology, but not convinced MRI is the best approach.
- The advantages of the proposed product relative to other FDA-approved imaging agents is not clear.
- Although iron labeling techniques are still being used by a few centers, the overall appeal for tracking cells by MRI has diminished in the scientific and clinical fields.
- There are still some minor technical concerns associated with hMSC labeling scaling up and lower Fe/cell values as compared to other magnetic labels (SPIO) that may impact cell-tracking capability due to lower SNR.
- Another concern is the lack of plans to communicate with FDA to confirm the submission requirements and to propose a plan to the regulators to get feedback. Since the applicants stated “for research use only” this may not be applicable but they discuss clinical use will be a future direction. It would be best to understand the required path for the intended product before starting large animal studies.
- The fate of Magnelles from both live and dead cells are not shown. It is expected that these Magnelles will be kicked out from the cell during division but the PI has not shown any studies related to this. The PI has also not planned any studies to show what will happen to the Magnelles released in the local tissue environment and assess the fate of iron release once cells are dead as well as how immune cells will handle these iron containing Magnelles.
- Most of the locally administered stem cells will die within a few days of implantation.
- The minimum number of cells that can be detected by *in vivo* MRI is not clear.
- Labeling efficiency has not been shown. Iron content per cells is similar to normal macrophages.
- True differential capacity of labeled stem cells needs to be shown. Although PI has mentioned it is underway by a grant from NIH.
- Local injection of labeled cells showed very limited low signal intensity on MRI. If a few cells migrate away from the sites of injection, MRI would not be able to detect the migration. So this is not tracking.
- None of the preliminary data showed long term tracking of live cells (max 7 days). 7 Days tracking can easily be done with In-111 labeled cells using SPECT. Tracking of labeled cells following IV injection is warranted.
- Figure 5 is not a true correlative study.
- In Figure 6 one time scanning using PET does not indicate a clearance study.
- *In vitro* migration and differential capacity of labeled MSC should be studied.
- An *in vivo* study should be done in a spinal cord injury model where bleeding will be present and MRI should differentiate administered cells, micro bleeding at the sites of injection as well as at the site of injury.
- There are immunological concerns that the magnelles will generate a strong immune response after multiple injections since they are derived from bacteria.
- It is not clear how a local injection could be detrimental to other major organs unless PI is considering the Magnelle infectious.

- There is no plan to do real biodistribution and toxicity studies after IV administration of different numbers of cells.
- A lot of uncertainty in planning and handing the project to 3rd party for development, fate and toxicity studies.
- Biostatistics are not well designed. Sample size calculation was not done.
- No timeline for pre-IND meeting or FDA approval process is presented.
- The imaging resolution needs to be higher.
- The sensitivity of clinical imaging is not high enough to use this technology - thus limiting its use.
- The lack of single cell sensitivity is a problem.
- There is significant concern about whether sensitivity can be achieved to answer key questions in cell therapy.
- A better understanding of sensitivity and capacity for differentiation between live vs. dead cells is needed.