TOTAL BUDGET: TRAN 2016, CYCLE 1

TIER 1 $36,777,876

TIER 2 $57,354,077

Application #	Title	Score	Median	SD	Low	High	Budget	Tier	T1	T2
TRAN1-08525	Process development for establishing an iPSC-based therapeutic candidate f	93	95	3	85	95	$7,377,384	1	13	0
TRAN1-08471	ASCENT- Advanced Superdonor Cellular Enteric Neuropathy Therapy	93	94	4	85	99	$7,139,913	1	14	0
TRAN1-08635	Placental Derived Natural Killer Cells to Target Solid Tumor Cancer Stem Cel	90	90	3	85	97	$2,368,818	1	15	0
TRAN1-08561	Personalized Cell Therapy for Diabetes	90	90	3	85	95	$5,000,000	1	14	0
TRAN1-08519	Overexpression of HexA/HexB by lentivector expression in blood cells to trea	90	90	1	85	90	$883,174	1	15	0
TRAN1-08552	Human Embryonic Stem Cell-Derived Neural Stem Cell Transplants in Amyot	89	90	4	80	95	$6,349,278	1	13	1
TRAN1-08522	2nd Generation Vaccine for the Treatment of Glioblastoma	87	90	7	65	90	$2,929,889	Deferred	12	2
TRAN1-08533	Stem Cell-Based iNKT Cell Therapy for Cancer	85	85	6	75	90	$7,659,309	1	11	4
TRAN1-08527	Ultrasound-mediated Stem Cell Activation: A Therapy for Tendon and Ligame	83	85	6	75	92	$4,501,965	2	7	6
TRAN4-08479	Integration defective lentiviral vector-mediated gene editing in human pluripot	79	80	2	75	80	$1,282,458	2	0	15
TRAN1-08504	Protease-Activated Receptor 2 as a Therapeutic Target to Induce Pancreatic	77	75	3	70	80	$2,416,834	2	0	15
TRAN4-08518	High throughput and high purity cell isolation for cell therapy development and	75	75	2	70	80	$1,286,185	2	0	15
TRAN4-08534	Real-time monitoring of stem cell differentiation for quality assurance in regen	75	70	7	65	85	$1,583,760	2	3	12
TRAN4-08598	Microelectrophysiological Assessment of Pharmacology using Labchip Electr	73	75	8	55	85	$1,204,432	2	1	14
TRAN1-08468	Autologous cell therapy for Parkinson's disease using iPSC-derived DA neuro	70	70	5	60	80	$7,971,025	2	0	14
TRAN4-08567	High-resolution, High-Sensitivity, Quantitative, and Functional in vivo Stem Ce	70	70	4	60	75	$1,449,817	2	0	15
TRAN3-08516	Improved bone repair by combining Reamer Irrigator Aspirator (RIA) bone gra	67	70	15	20	75	$1,515,542	2	0	15
TRAN4-08575	A Tool to Quantitate Antigen-Specific T cell populations for Engineered Stem	62	60	7	50	78	$1,037,632	2	0	15
TRAN2-08510	MRI-based measurements of pH in spinal discs: A diagnostic tool for stem ce	62	62	8	50	75	$1,711,631	2	0	14
TRAN1-08501	Human iPSC-derived GABAergic Interneuron Progenitors for Alzheimer's Dis	61	65	11	40	70	$5,210,057	2	0	15
TRAN4-08607	In situ forming hydrogels for effective stem cell delivery and engraftment after						$1,519,920	2	0	15
TRAN2-08615	PET imaging probes to monitor critical steps in stem cell-based therapies for						$1,843,200	2	0	15
TRAN3-08574	Enhanced Engraftment of Transplanted Stem Cells using Growth Factor Sequ						$2,448,988	2	0	15
TRAN1-08584	Targeted nanotherapeutics to eradicate acute leukemia stem cells						$7,301,881	2	0	15
TRAN3-08555	Novel Device for Stem Cell Delivery into Brain Tumors						$2,152,041	2	0	15
TRAN1-08645	Human Embryonic Stem Cell-Derived Neural Stem Cells for Severe Spinal Co						$5,603,017	2	0	14
TRAN1-08511	Preclinical studies using a stably genetically-engineered hESC-derived A9 ne						$4,221,692	2	0	15
TRAN1-08586	Selective inhibitor nanoparticles targeting liver cancer stem cells						$1,092,000	2	0	15

Public Review Summary
PA TRAN: Partnering Opportunity for Translational Research Projects

Application #	TRAN1-08468
Title (as written by the applicant)	Autologous cell therapy for Parkinson's disease using iPSC-derived DA neurons
Translational Candidate (as written by the applicant)	Autologous dopaminergic neurons derived from patient-specific induced pluripotent stem cells
Area of Impact (as written by the applicant)	Parkinson's disease
Mechanism of Action (as written by the applicant)	The proposed candidate is intended to replace the lost dopaminergic (DA) neurons in the brains of Parkinson's disease patients. It is estimated that by a time patients are diagnosed with Parkinson's disease, they have already lost over 50% of their DA neurons in their brains. Earlier studies using fetal tissue demonstrated proof of principle for cell replacement therapy. We will use highly qualified patient-specific DA neurons to eliminate the need for immunosuppression.
Unmet Medical Need (as written by the applicant)	Currently, there is no treatment for Parkinson's disease that can stop the progressive degeneration or replace lost neurons. Current treatments, including pharmacological intervention and deep brain stimulation only provide limited relief and decline in efficacy with time.
Project Objective (as written by the applicant)	A well-prepared pre-IND meeting.
Major Proposed Activities (as written by the applicant)	• Assess in vivo behavior with a dosing study, combination tumor/biodistribution/toxicity study and cell delivery using a large animal model. • Characterize comparability between patient cell lines, determine final product and develop in process and release testing. • Transfer technologies, protocols and cells to a cGMP facility for banking and cell production under cGMP conditions.
Statement of Benefit to California (as written by the applicant)	Thousands of Californians suffer from the degenerative effects of Parkinson's disease, a disease for which there is no cure. There is hope, however, that stem cells could provide the key to providing long-term relief. Our study seeks to treat patients with cells derived from their own stem cells, a process which could be applied to other diseases such as diabetes and heart disease and could potentially be used to the benefit of many of the citizens of California.
Funds Requested	$7,971,025
GWG Recommendation	***Tier 2 – Not recommended for funding.***

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.

Median	70
Standard Deviation	5
Highest	80
Lowest	60
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available.	0
Tier 2 (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?	8	2	4
Is the rationale sound?	7	3	4
Is the proposal well planned and designed?	2	9	3
Is the proposal feasible?	1	6	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

- The overall plan of producing autologous iPSC-derived A9 dopaminergic neurons is supported by data and discussions that have been on-going in the Parkinson's Disease (PD) research community. An autologous approach is expected to be feasible in PD patients.
- The current team is well-suited for the cell production component of the study.
- The project has significance and has sufficient impact.

Concerns

- Although the strategy is promising, this proposal is not yet ready for translation. It is missing key methodological details. For example, the development plan and logistics have major flaws. There is also a lack of preliminary efficacy data.
- There are questions about the nine iPSC lines that have been derived to date. The program intends to use these lines to establish cGMP banks for future DA neuron production. However, the reprogramming method raises concerns about the impact on suitability of these cells for clinical use. The upcoming meeting with the FDA should provide more insight on the project direction if the applicant provided enough information to allow the FDA to make a clear assessment.
- There was not sufficient data on cell line to cell line variability. Only two iPSC lines were taken forwarding into the ongoing proof-of-concept studies. More data must be gathered to understand key variability (mutations, off-target cell types, residual iPSCs) and the potential impact on safety.
- The designs for the animal studies do not match the attached protocols. The large animal pilot delivery study in Table 10 is a large study and should not be conducted until the product is defined and a delivery device chosen. This is a definitive IND enabling study. The proposed protocol using the large animal model is appropriate.
- The pilot tumorigenicity study has too few animals for meaningful interpretation. There is no description of what is considered to be a tumor in the safety studies. What markers will be used? If there is slow proliferation or low grade proliferation, will that be considered safe? What is the cut off?
- The applicant should have provided more information on how the whole genome sequencing data would be analyzed to determine whether mutations represent a safety risk. This is a big challenge given that there are likely a significant number of background mutations that arise from the culture.
- There is no evidence that the produced cells can be functional, as expected; an in vivo test to show demonstrated production of dopamine or a proposed test would strengthen this proposal.
- The team needs added expertise for the behavioral analysis study.
- There is no description of what is considered to be a tumor in the safety studies. What markers will be used? If there is slow proliferation or low grade proliferation, will that be considered safe?
- The regulatory strategy appears to be incomplete in its design. The product design must be locked in before proceeding with the FDA.

Additional Comments

- The team should be encouraged to resubmit because the project, if successful, has potential for significant impact on PD.
- The investigators should add one outcome that is a measure of DA levels in cultures cells and in the medium under basal and stimulated release conditions.
- Preliminary data that shows the cells can provide meaningful outgrowth would strengthen the proposal.
- Reviewers suggested that convincing data from an immunocompromised or humanized animal model showing maintenance of phenotype and differentiation could improve the proposal.
- Reviewers recommended that the team resolve these issues and resubmit for the appropriate CIRM program.

Public Review Summary
PA TRAN: Partnering Opportunity for Translational Research Projects

Application #	TRAN1-08471
Title (as written by the applicant)	ASCENT- Advanced Superdonor Cellular Enteric Neuropathy Therapy
Translational Candidate (as written by the applicant)	ASCENT - Advanced Superdonor Cellular Enteric Neuropathy Therapy, is a donor progenitor cell population that replaces the enteric nervous system.
Area of Impact (as written by the applicant)	ASCENT would treat enteric neuropathies including Hirschsprung disease and total intestinal aganglionosis which currently have no direct therapy
Mechanism of Action (as written by the applicant)	Our goal is to develop an allogeneic “off the shelf” cellular therapy to treat enteric neuropathies before surgical interventions are needed or to rescue patients in whom effects of the ENS defect persist. We propose to generate a cellular therapy from the starting material of “superdonor” human iPS cell lines. ASCENT - Advanced Superdonor Cellular Enteric Neuropathy Therapy, is a donor progenitor cell population that, after transplantation in vivo, replaces absent functional ENS components.
Unmet Medical Need (as written by the applicant)	There are no direct therapies for enteric neuropathies and ASCENT would be the first cellular therapy for a broad class of severe disease including Hirschsprung disease and other enteric neuropathies that are morbid and mortal.
Project Objective (as written by the applicant)	Successful Pre-IND meeting with the FDA.
Major Proposed Activities (as written by the applicant)	• Manufacture ASCENT to supply the proposed studies that will assess safety and efficacy. • Determine the optimal dosing of ASCENT as well as assess clinical safety. • Completion of nonclinical safety studies in order to schedule and complete a Pre-IND meeting.
Statement of Benefit to California (as written by the applicant)	Enteric neuropathies cost the state of California hundreds of millions of dollars and cost the people of California more because of the severe problems including death that result from this class of diseases. This proposal benefits California in two ways: by supporting science and the industries in California that grow from ongoing investigation, but also by reducing the medical costs and suffering of patients with enteric neuropathic conditions with development of a novel and needed therapy.
Funds Requested	$7,139,913
GWG Recommendation	***Tier 1 – Exceptional merit and warrants funding, if funds are available.***

Final Score: 93

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.

Median	94
Standard Deviation	4
Highest	99
Lowest	85
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	14
Tier 2 (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?	13	0	1
Is the rationale sound?	13	0	1
Is the proposal well planned and designed?	13	0	1
Is the proposal feasible?	12	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

- The grant application is excellent and includes a great team. Reviewers praised the team as having great expertise and noted that the team could perhaps be the best in the world for this indication.
- The approach received praise from the review panel.
- The unmet medical need is significant and the proposed therapy holds translation potential.
- The product development plan is excellent and well thought out.

- The human feasibility data is very impressive and coupled with the complete preliminary data package, there is a strong basis to conclude that the approach has a high likelihood of success.
- The investigator is outstanding.
- The regulatory issues are wonderfully addressed.

Concerns

- Concerns exist regarding the "superdonor" concept and its potential for immune rejection/reaction, even with immune suppression.

Additional Comments

- The team should consider an acceleration of this program and to consider preparation of a pre-IND meeting within the first year.
- An opportunity exists to streamline the toxicity program.

Public Review Summary
PA TRAN: Partnering Opportunity for Translational Research Projects

Application #	TRAN1-08501
Title (as written by the applicant)	Human iPSC-derived GABAergic Interneuron Progenitors for Alzheimer's Disease Treatment
Translational Candidate (as written by the applicant)	Human iPSC-derived GABAergic interneuron progenitors
Area of Impact (as written by the applicant)	Alzheimer's disease and related conditions
Mechanism of Action (as written by the applicant)	Transplantation of human iPSC-derived GABAergic inhibitory neuron progenitors to replace the lost GABAergic neurons in AD brains
Unmet Medical Need (as written by the applicant)	As a complex disease that damages the hippocampus, a brain region essential for cognition, Alzheimer's disease presents unique challenges for developing traditional therapies. iPSCs provide a way to generate brain cells for cell-replacement therapy.
Project Objective (as written by the applicant)	Pre-IND
Major Proposed Activities (as written by the applicant)	• Establish a robust differentiation protocol for deriving GABAergic progenitors from human iPSCs. • Short-term efficacy and safety tests of human iPSC-derived GABAergic interneuron progenitors. • Long-term efficacy and safety tests of human iPSC-derived GABAergic interneuron progenitors.
Statement of Benefit to California (as written by the applicant)	Alzheimer's disease (AD) is the leading cause of dementia in California. Currently, there are over 480,000 AD patients in California—more than in any other US state—costing over $20 billion USD in healthcare each year. This research project focuses on developing cell-replacement therapies for AD. Successful completion of this research could help to improve the health of Californians and reduce the adverse impact of AD, thereby increasing productivity and enhancing quality of life.
Funds Requested	$5,210,057
GWG Recommendation	***Tier 2 – Not recommended for funding.***

Final Score: 61

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.

Median	65
Standard Deviation	11
Highest	70
Lowest	40
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available.	0
Tier 2 (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?	9	2	4
Is the rationale sound?	8	2	5
Is the proposal well planned and designed?	1	8	6
Is the proposal feasible?	2	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

- This research proposal is a very interesting approach to developing a cell therapy for treating Alzheimer's disease.
- The animal models and data presented were compelling for further development; in particular, the preliminary data demonstrate improved memory and mental acuity which is a strength of the application.
- This is an important and worthy area of research.
- The significance is clear and the outcome of this application could be very impactful if successfully carried out.

- The application is based on strong science.

Concerns

- The team is a concern.
  - The team is missing some of the expertise necessary for translation of this project.
  - The team is insufficient to advance the project to the preIND stage.
  - The team could benefit from a CMC regulatory consultant to provide input on the manufacturing and QC side of the project as it moves into IND-enabling animal studies.
- The proposal is overambitious.
- The project is not suitable for translational research without the right partners.
- There is no discussion of prepre-IND or pre-IND submissions other than the applicant commenting that after completing the studies they will initiate discussions with FDA on how to move the project to IND-enabling studies.
- Other aspects of cell administration and immunosuppression should be carefully considered to make sure they are inline with what will be used in the human clinical trial. For example, it is not clear that the Ab cocktail will work in humans.
- Cell cryopreservation and handling should be worked out.
- The lack of regulatory input weakens the design of the research plan.
- This is a sound R01-level basic science project, but it is not ready for translation and translational aspects of the project are lacking from the application.
- The approach as described in the application may not work in human.

Additional Comments

- No relevant comments were made by the GWG.

Public Review Summary
PA TRAN: Partnering Opportunity for Translational Research Projects

Application #	TRAN1-08504
Title (as written by the applicant)	Protease-Activated Receptor 2 as a Therapeutic Target to Induce Pancreatic Beta-Cell Regeneration
Translational Candidate (as written by the applicant)	The translational candidate is a peptide agonist of the Protease-Activated Receptor 2 GPCR
Area of Impact (as written by the applicant)	Type I diabetes
Mechanism of Action (as written by the applicant)	The proposed candidate will induce the formation of new pancreatic beta-cells.
Unmet Medical Need (as written by the applicant)	Inducing the formation of new pancreatic beta-cells has the potential to be part of a definitive treatment for type I diabetes.
Project Objective (as written by the applicant)	Develop novel type I diabetes therapy
Major Proposed Activities (as written by the applicant)	• Define optimal protocol for drug delivery. • Demonstrate efficacy with human cells in model system in vivo. • Demonstrate safety in animal model.
Statement of Benefit to California (as written by the applicant)	Type I diabetes is a disease that afflicts about 1 in 300 individuals in the USA, including California. The proposed research is directed at developing a definitive treatment for that disease.
Funds Requested	$2,416,834
GWG Recommendation	***Tier 2 – Not recommended for funding.***

Final Score: 77

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.

Median	75
Standard Deviation	3
Highest	80
Lowest	70
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available.	0
Tier 2 (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?	8	3	4
Is the rationale sound?	6	3	6
Is the proposal well planned and designed?	1	4	10
Is the proposal feasible?	0	9	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

- The proposal's high level of innovation and exciting biology are sources of enthusiasm.
- The proposal contains a novel, potentially paradigm-shifting idea that is supported by strong preliminary data. The approach has a good rationale and has merit. If successful, this product would create a means of producing autologous functioning beta cells from existing precursors in individuals with type I diabetes.
- The proposal is well constructed.

Concerns

- The chief concern is that this proposal does not contain studies that will lead to a pre-IND meeting in the proposed 30-month time frame.

- A true stem cell component is lacking. The drug is expressly thought NOT to be de-differentiating alpha cells. Rather, it is proposed to lead to direct transdifferentiation of alpha cells to beta cells, and then on to delta cells without going through a stem cell intermediate.

- Reviewers expressed concern that this peptide may activate other cell types and cause more insulin production that may cause hypoglycemia. Reviewers stressed that further assessment of off-target (non-pancreas) PAR-2 effects is needed.

- It is not clear the team has the best molecule; greater sophistication in drug discovery is needed. For example, reviewers expressed reservations about fundamental issues such as pharmacokinetics and ADME (adsorption, distribution, metabolism, excretion) that require additional consideration.

- The team would be well served to form ties or at the least get more hands-on participation from individuals with development and commercial experience from the biopharma industry. The team also lacks regulatory direction and would benefit from this expertise.

- Although a number of the reviewers believed the rationale to be sound, the feasibility is the project still in question since there are a number of unanswered questions.

- Adequate immune suppression/modulation technology does not exist to address some of the questions regarding feasibility.

Additional Comments

- This project is not mature enough for translation or a pre-IND meeting. CIRM's Translation Program may not be the right mechanism for funding this proposal at this moment.

- Reviewers suggested that this team seek another funding opportunity at an earlier stage of development through CIRM or another comparable program.

Public Review Summary
PA TRAN: Partnering Opportunity for Translational Research Projects

Application #	TRAN1-08511
Title (as written by the applicant)	Preclinical studies using a stably genetically-engineered hESC-derived A9 neural progenitor for therapeutic development in Parkinson's disease
Translational Candidate (as written by the applicant)	Human ESC-derived Neural progenitors that are genetically programmed to express MEF2C
Area of Impact (as written by the applicant)	Moderate to Severe Parkinson's disease, where L-DOPA or other treatments are no longer effective
Mechanism of Action (as written by the applicant)	Our therapeutic candidate -- a genetically programmed human embryonic stem cell (hESC)-derived neural progenitor cell -- offers a potentially curative therapy for Parkinson's disease (PD) by producing dopamine (DA) neurons, the major cell type lost in PD. Transplantation of progenitor cells that are programmed to become DA neurons will replace cells lost in PD, thus stopping or slowing progression of the disease.
Unmet Medical Need (as written by the applicant)	Currently there is no cure for Parkinson's diseases (PD), which affects approximately one million people in the United States and about ten million worldwide. This work aims at developing a potentially curative cell replacement therapy in PD.
Project Objective (as written by the applicant)	Completion of Pre-IND meeting with the FDA
Major Proposed Activities (as written by the applicant)	• Manufacturing of cGMP qualified Stem Cell Bank and perform quality control (QC) tests. • Preclinical dose-response efficacy & Safety evaluation of clinical grade MEF2CA-hNPCs in PD small and large animal models. • Completion of pre-IND meeting with the FDA.
Statement of Benefit to California (as written by the applicant)	Many of the million Parkinson's disease (PD) patients in the US reside in California. Current symptomatic treatments become ineffective in most patients within about ten years. This is a devastating time for both patients and their families. Our cell-based therapy will restore production of dopamine and/or the ability to effectively use L-DOPA medicine, which will greatly improve the lives of these patients. This gives California a unique opportunity to be a word leader in this area.
Funds Requested	$4,221,692
GWG Recommendation	***Tier 2 – Not recommended for funding.***

Final Score: 41

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.

Median	40
Standard Deviation	11
Highest	60
Lowest	25
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available.	0
Tier 2 (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?	4	9	1
Is the rationale sound?	0	14	0
Is the proposal well planned and designed?	0	13	1
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

- It will be feasible to develop an H9-based allogeneic cell therapeutic to treat PD patients. The team is using the correct A9 midbrain dopaminergic neuron.

Concerns

- Unclear if the MEF2 gene expression provides an advantage over non-modified A9 DA neurons.
- Data on survival and integration of the A9 DA cells was not compelling. There was not any staining for TH+ cells.

- Overall concerns regarding the quality of data supporting the use of these cells in PD patients was the main overriding negative aspect of the proposal.
- On the CMC side, the lentivirus source and quality was an issue. If GFP is to be used for cell selection in the clinical production (unclear), this could obviously be a concern from an immunogenicity point of view.
- The current cell bank has 50 vials and 8-10 would have been used for the current planned animal studies. This raises a big concern regarding the size of the bank and ability to support future clinical production. It would be better to create a cGMP Master and Working Cell Bank now and make sure that it is large enough to support the pre-clinical animal studies through to commercial launch. Having to make another bank to continue supply will cause some major regulatory issues.
- The applicant proposes a large number of large animal studies, but does not include clear goals. These studies appear to be premature.
- Efficacy is not yet convincing.
- Statistical analyses proposed are not strong.
- Preliminary data is not compelling.
- Proposal has problems with experimental plan; the data is not convincing, and feasibility is not certain.

Additional Comments

- No relevant comments were made by the GWG.

Public Review Summary
PA TRAN: Partnering Opportunity for Translational Research Projects

Application #	TRAN1-08519
Title (as written by the applicant)	Overexpression of HexA/HexB by lentivector expression in blood cells to treat Tay-Sachs and Sandhoff disease
Translational Candidate (as written by the applicant)	Autologous hematopoietic stem cells transduced with a lentiviral vector expressing wild type human HexA and HexB.
Area of Impact (as written by the applicant)	The therapeutic candidate would halt disease progression in Tay-Sachs and Sandhoff disease patients who have no curative or ameliorating treatment.
Mechanism of Action (as written by the applicant)	Wild type HexA and HexB will be delivered to affected neurons through cross-correction by immune cells derived from lentivector transduced hematopoietic stem cells. This will result in a renewed degradation of accumulated GM2-gangliosides, thus, rescuing affected neurons and halting disease progression. The combination of gene therapy and hematopoietic stem cells offers a promising approach for constitutive and life-long delivery of HexA and HexB to affected neurons.
Unmet Medical Need (as written by the applicant)	Tay-Sachs and Sandhoff disease are characterized by an accumulation of GM2-gangliosides due to a defective β-N-acetlyhexosaminidase protein leading to progressive, fatal neurodegeneration. There is no cure or corrective therapy for TS or SD and supportive care only marginally prolongs patient lives.
Project Objective (as written by the applicant)	Our objective is to have a pre-IND meeting.
Major Proposed Activities (as written by the applicant)	• Evaluate the in vitro safety and efficacy of HexA/HexB lentivector transduced human CD34+ HPC. • Evaluate the safety of HexA/HexB lentivector transduced hematopoietic stem cells for engraftment, multi-lineage hematopoiesis, and tumorigenicity. • Evaluate the efficacy of HexA/B lentivivector transduced hematopoietic stem cells to decrease GM2 levels, increase motor function, and prolong lives.
Statement of Benefit to California (as written by the applicant)	Tay-Sachs (TS) and Sandhoff disease (SD) are classified as rare and orphan diseases that affect patients as infants, juveniles, and adults. Currently there is no cure or effective treatment for TS or SD and supportive care can only marginally prolong the lives of patients. Our therapy would halt the progression of these diseases and after demonstrating success, would open the door for the use of hematopoietic stem cell gene therapy for the treatment of other lysosomal storage diseases.
Funds Requested	$883,174
GWG Recommendation	***Tier 1 – Exceptional merit and warrants funding, if funds are available.***

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.

Median	90
Standard Deviation	1
Highest	90
Lowest	85
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available.	15
Tier 2 (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	5
Is the rationale sound?	10	0	5
Is the proposal well planned and designed?	10	0	5
Is the proposal feasible?	9	0	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 strong clinical need and great clinical significance to develop a treatment for a fatal disease that has no cure.
- The rationale is strong and compelling.
- Good preliminary data was provided in the proposal.
- The proposal is a well designed, and the existing clinical data shows feasibility. In particular, the proof of principle provided from leukodystrophy is a strength.

- This is an excellent investigative team.
- The team has access to all necessary reagents and resources to carry out the work.

Concerns

- The stage of vector development is not completely clear. Milestone 1 includes the manufacturing of the vector. Will this be done using a method that will transition into GMP manufacturing?
- The request for support for 0.75 FTE seems low given the amount of work to be performed in a relatively short time.

Additional Comments

- It would be beneficial to hold a pre-pre-IND meeting with the FDA to review the experimental plan to avoid potential future regulatory issues.

Public Review Summary
PA TRAN: Partnering Opportunity for Translational Research Projects

Application #	TRAN1-08522
Title (as written by the applicant)	2nd Generation Vaccine for the Treatment of Glioblastoma
Translational Candidate (as written by the applicant)	It is a peptide conjugated to KLH and used as an anti-cancer vaccine.
Area of Impact (as written by the applicant)	This is a better optimized, more robust vaccine that aspires to greatly improve glioblastoma patient survival over the current vaccine.
Mechanism of Action (as written by the applicant)	The vaccine stimulates B cell and T cells. We have found this may be mediated through more extensive processing of our candidate by the proteasome. Once these immune system cells are stimulated, they will attack tumors expressing EGFRvIII.
Unmet Medical Need (as written by the applicant)	Glioblastoma is the most common and deadly brain tumors: median survival is only 14-16 months and five-year survival of 9%. Therapies are desperately needed to significantly prolong survival. Our 2nd generation vaccine shows a 2-fold increase in survival over a vaccine that has already shown promise.
Project Objective (as written by the applicant)	Pre-IND meeting and readiness for GMP manufacture.
Major Proposed Activities (as written by the applicant)	• Synthesis of the peptide under GMP-like conditions and conjugation of the peptide to KLH under GMP-like conditions. • Confirming structure and biologic activity of the conjugate, and confirming it has an excellent safety profile in toxicology tests. • Planning meetings with the FDA and then preparing the Phase I trial protocol in anticipation of filing IND
Statement of Benefit to California (as written by the applicant)	Californians will benefit from this research project in several significant ways. The research will take place in California and directly benefit the economy through hiring of employees and purchase of supplies and reagents. If the therapeutic is successful, it will extend the long-term survival rates for Californians with glioblastoma. If it is commercialized, profits derived from the vaccine will further improve the California economy and lower costs to uninsured patients.
Funds Requested	$2,929,889
GWG Recommendation	***Tier 1 – Exceptional merit and warrants funding, if funds are available.***

Final Score: 87

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.

Median	90
Standard Deviation	7
Highest	90
Lowest	65
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available.	12
Tier 2 (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?	9	0	5
Is the rationale sound?	9	0	5
Is the proposal well planned and designed?	10	0	4
Is the proposal feasible?	10	0	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

- Glioblastoma represents an important and unmet medical need.
- This approach could also be relevant to other tumors, thereby increasing its potential for impact.
- There is a very well thought out plan. A strong scientific rationale supports the proposal.
- The proposal included excellent preliminary data.
- This is a great team that has achieved significant accomplishments.

Concerns

- KLH- peptide approach may not work in the immune privileged environment of the brain. Peptide based vaccine will not work for a glioblastoma vaccine. Previous studies with different cocktail of peptides failed.

Additional Comments

- No relevant comments were made by the GWG.

Public Review Summary
PA TRAN: Partnering Opportunity for Translational Research Projects

Application #	TRAN1-08525
Title (as written by the applicant)	Process development for establishing an iPSC-based therapeutic candidate for Canavan disease
Translational Candidate (as written by the applicant)	Genetically-corrected patient iPSC-derived neural progenitor cells, which have demonstrated efficacy to correct disease phenotype in a CD mouse model.
Area of Impact (as written by the applicant)	This candidate has the potential to develop into a therapy for Canavan disease, a fatal neurological disease that has no cure or standard treatment.
Mechanism of Action (as written by the applicant)	The proposed candidate is intended to correct disease phenotype through a cell replacement approach. Moreover, the derivative of the genetically-corrected iPSCs will provide ASPA enzymatic activity, which is deficient in Canavan disease patients. The ASPA enzyme will be able to reduce NAA level, which accumulates to a toxic level in patient brains to cause sponge degeneration.
Unmet Medical Need (as written by the applicant)	There is neither cure nor a standard course of treatment for Canavan disease. The therapeutic candidate we propose to develop in this study has the potential to lead toward the development of a cell replacement therapy for this disease.
Project Objective (as written by the applicant)	Pre-IND meeting and readiness for manufacturing.
Major Proposed Activities (as written by the applicant)	• Establishing a cGMP-compatible process in order to transfer the therapeutic candidate to manufacturing. • Determining the in vivo efficacy and safety of the therapeutic candidate prepared using the cGMP-compatible process in CD mice. • Preparing and conducting a pre-IND meeting with the FDA.
Statement of Benefit to California (as written by the applicant)	California is estimated to have ~12% of all cases of Canavan disease in the U.S. Besides the emotional and physical pain this disease inflicts on families, it produces a medical and fiscal burden in California that is larger than any other states. The proposed therapeutic candidate will represent 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 cell replacement therapy.
Funds Requested	$7,377,384
GWG Recommendation	***Tier 1 – Exceptional merit and warrants funding, if funds are available.***

Final Score: 93

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.

Median	95
Standard Deviation	3
Highest	95
Lowest	85
Count	13

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available.	13
Tier 2 (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	3
Is the rationale sound?	10	0	3
Is the proposal well planned and designed?	9	0	4
Is the proposal feasible?	9	0	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

- Canavan disease is a devastating pediatric orphan disease representing an unmet medical need that desperately needs progress since no alternative treatments are available.
- Although an autologous, gene corrected cell therapy will be challenging, the disease is a good choice from a risk-benefit perspective as the high benefit/risk ratio is favorable.
- The selected drug target is great.
- The proposed experimental design is elegant and the plan is well thought out in every respect.
- This is a great team that is qualified to undertake the proposed studies.

- The proposal included excellent and strong preliminary data demonstrating efficacy in an appropriate animal model.
- The proposal and its objectives are consistent with CIRM's mission to accelerate stem cell treatments to patients with unmet medical needs.

Concerns

- The team should consider a plan of how genome sequencing data will be analyzed and how this information will be evaluated for each cell line. This is a big challenge given the amount of data and the level of background mutations from culture relative to the CRISPR/Cas9 off-target effects.
- The proposal should have more clarity regarding the key studies and criteria that will be used to select either lenti-ASPA or CRISPR/Cas9 gene editing as the method of choice for producing cells for pre-clinical animal testing and future human clinical trials.

Additional Comments

- The team should be careful to define how the cells will likely be formulated and handled (cryopreservation, thaw/wash, injection) for human clinical trials. Ideally, these same methods will be utilized for the preclinical animal studies to help establish the validity of the selected formulation and handling procedures.

Public Review Summary
PA TRAN: Partnering Opportunity for Translational Research Projects

Application #	TRAN1-08527
Title (as written by the applicant)	Ultrasound-mediated Stem Cell Activation: A Therapy for Tendon and Ligament Injuries
Translational Candidate (as written by the applicant)	An ultrasound system and a therapeutic gene for tendon and ligament repair.
Area of Impact (as written by the applicant)	Ligament and tendon tears that require surgical reconstruction.
Mechanism of Action (as written by the applicant)	The candidate is intended to accelerate the integration of the ligament graft to its insertion in bone. If successful, it will enable the patient to quickly return to active life and sports activities.
Unmet Medical Need (as written by the applicant)	Current surgical techniques suffer from pronged periods of reconstructed ligament/tendon healing during which the patient's physical and sports activities are limited or prohibited.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Establish ultrasound protocol for gene delivery to ACL graft insertion. • Test the therapeutic candidate in a pig model of ACL reconstruction. • Develop a clinical plan and conduct a pre-IND meeting.
Statement of Benefit to California (as written by the applicant)	In 2014, 290,000 emergency room visits were reported in California due to sports injuries. Many of these injuries involve ligaments and tendons. For example, ACL injury has an annual incidence of more than 200,000 cases with ~100,000 of these knees reconstructed annually, as reported in 2008. Physical rehabilitation after ACL surgery may take several months to a year. If successful the proposed therapy will help many Californians to return to normal and sports activities, rapidly.
Funds Requested	$4,501,965
GWG Recommendation	***Tier 2 – Not recommended for funding.***

Final Score: 83

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.

Median	85
Standard Deviation	6
Highest	92
Lowest	75
Count	13

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available.	7
Tier 2 (1-84): Not recommended for funding.	6

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	1	5
Is the rationale sound?	8	1	4
Is the proposal well planned and designed?	8	0	5
Is the proposal feasible?	8	0	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 proposal contains a clever and innovative technology coupled with with tools that are already used in the clinic.
- In particular, the use of ultrasound to introduce DNA and matrix technology to bring MSC to site of surgery is innovative.
- The proposed therapeutic addresses an unmet medical need.

- The team is excellent and has significant experience. The team has a high probability of reaching a pre-IND meeting following the proposed aggressive timeline.
- The proposal is well written. In particular, the presentation of the translational plan is well conceived.
- The preliminary data is compelling and gives credence to the proposal's feasibility.
- The feasibility is strengthened by the techniques that were established in the lab.
- The proposed large animal model is appropriate and a strength of the proposal.
- The well designed studies are a strength.

Concerns

- Although the studies are generally well designed, concerns exist regarding the lack of the standardization of the dosing of the plasmids as well as the control and persistence of the plasmid DNA.
- There is limited data regarding the healing effects of the scaffold. Inadequate justification for the choice of scaffold is given.
- The calcification of surrounding tissues and other ligaments is a concern. Forming bone in the tendon is very painful, and this issue is not adequately addressed.
- Reviewers expressed caution regarding off-target transfection and the ability to control the duration/dose of BMP expression.
- The investigators did not adequately describe the actual burden of illness---definition of failure; failure rate at different sites; overall impact of failure; etc.

Additional Comments

- The FDA should be consulted early in the process to determine if additional safety data or other animal models will be required for an IND filing.

Public Review Summary
PA TRAN: Partnering Opportunity for Translational Research Projects

Application #	TRAN1-08533
Title (as written by the applicant)	Stem Cell-Based iNKT Cell Therapy for Cancer
Translational Candidate (as written by the applicant)	Lenti/iNKT-sr39TK Modified Autologous Human CD34+ Hematopoietic Stem Cells (HSCs)
Area of Impact (as written by the applicant)	The targeted area of impact for the candidate is cancer therapy, in particular cancers that are lacking existing effective treatments.
Mechanism of Action (as written by the applicant)	The proposed candidate will generate therapeutic levels of invariant natural killer T (iNKT) cells in cancer patients, helping them to battle their deadly diseases. These iNKT cells can both directly kill tumor cells, and activate other immune cells like natural killer (NK) cells and cytotoxic T cells (CTLs) to eradicate tumor.
Unmet Medical Need (as written by the applicant)	Despite the existing therapies, cancer patients still suffer from the ineffectiveness of these treatments, their toxicities, and the risk of relapse. Our proposed Stem Cell-Based iNKT Cell Therapy represents a novel therapy for cancer that can potentially help many cancer patients.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Conduction of Preclinical Studies. • Development of a Clinical Trial Protocol. • Preparation for and Conduction of a Pre-IND Meeting with the FDA.
Statement of Benefit to California (as written by the applicant)	Cancer is a leading threat to public health in the United States and in the State of California. In 2015, it is estimated that over 160,000 Californians can be diagnosed with cancer. Cancer is the second leading cause of death in California, and also brings devastating economic impacts to the State. Our proposed Stem Cell-Based iNKT Cell Therapy, if successful, has the potential to save the lives of Californians and reduce the economic burden for cancer treatment.
Funds Requested	$7,659,309
GWG Recommendation	***Tier 1 – Exceptional merit and warrants funding, if funds are available.***

Final Score: 85

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.

Median	85
Standard Deviation	6
Highest	90
Lowest	75
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available.	11
Tier 2 (1-84): Not recommended for funding.	4

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	4
Is the rationale sound?	7	2	6
Is the proposal well planned and designed?	9	1	5
Is the proposal feasible?	7	2	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

- Preliminary data is promising and provide a good basis on which to proceed with the proposed study.
- A proposal of potentially high significance with an excellent team of investigators and environment.
- The team is excellent and there is confidence that they will be able to resolve issues that arise.

Concerns

- There are safety concerns related to potential widespread expression on the transgene. NK specific expression is needed.
- The proposed suicide gene is not suitable for the clinic since it is immunogenic and only active in rapidly dividing cells.
- The mechanism of iNKT cell generation from transduced CD34+ cells is not well-understood and possess a risk that it may not be reproducible upon scale-up and translation into the clinic.
- Animal model data is not strong and data demonstrating target cell killing was lacking.

Additional Comments

- The team would benefit from pre-pre-IND meeting with the FDA to review safety concerns.
- The vector construct will need to be modified before submission of an IND.

Public Review Summary
PA TRAN: Partnering Opportunity for Translational Research Projects

Application #	TRAN1-08552
Title (as written by the applicant)	Human Embryonic Stem Cell-Derived Neural Stem Cell Transplants in Amyotrophic Lateral Sclerosis
Translational Candidate (as written by the applicant)	Spinal cord injections of human embryonic stem cell (hESC)-derived allogeneic neural stem cells (heNSCs) for treatment of ALS
Area of Impact (as written by the applicant)	Treatment of Amyotrophic Lateral Sclerosis (ALS)
Mechanism of Action (as written by the applicant)	Although the exact molecular mechanism of action is unknown, extensive research supports the concept that the behavior of defective astrocytes is key to the death of motor neurons and the development and progression of ALS. Allogeneic neural stem cells (heNSCs) injected into the spinal cord migrate and differentiate into functional astrocytes which can protect and support endogenous neurons, preventing further motor neuron loss and disease progression.
Unmet Medical Need (as written by the applicant)	ALS is a disease for which there is literally no currently effective therapy. While there are some mild palliative approaches to treatment, in virtually all cases the diagnosis of ALS is effectively equivalent to a death sentence.
Project Objective (as written by the applicant)	Pre-IND meeting with the FDA
Major Proposed Activities (as written by the applicant)	• Scale up manufacturing of product for proposed studies and perform product characterization, function and efficacy testing. • Develop in vitro methods for testing product function, efficacy and safety. • Perform pilot in vivo tests for determination of cell survival, fate, safety. Develop and standardize in vivo and in vitro tumorigenicity methods.
Statement of Benefit to California (as written by the applicant)	ALS is a disease for which there is literally no currently effective therapy. While there are some mild palliative approaches to treatment, in virtually all cases the diagnosis of ALS is effectively equivalent to a death sentence. Clearly, in view of the dire prospects facing these patients, aggressive action on multiple, parallel therapeutic fronts is critical. It is important in our view to develop an aggressive set of cell therapy programs and have multiple “shots on goal” in parallel.
Funds Requested	$6,349,278
GWG Recommendation	***Tier 1 – Exceptional merit and warrants funding, if funds are available.***

Final Score: 89

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.

Median	90
Standard Deviation	4
Highest	95
Lowest	80
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available.	13
Tier 2 (1-84): Not recommended for funding.	1

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	2
Is the rationale sound?	10	2	2
Is the proposal well planned and designed?	11	1	2
Is the proposal feasible?	10	1	3

Review 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

- Overall, the goal of developing a potential new cell therapy for ALS is a very worthwhile undertaking that could have a positive impact on outcomes for ALS patients.
- This proposal is a good project with high translational potential.
- There is a strong unmet medical need.
- The proposal contains strong preliminary data and is well designed to meet its goal of holding a pre-IND meeting.

- The proposed stem cell source provides an alternative cell source for evaluation in ALS patients.
- The high level of collaboration throughout the project is very impressive. The team is superb.

Concerns

- The team should carefully review the master cell bank/working cell bank size and manufacturing process to ensure that the manufacturing process is in line with the process that will be used for human clinical trials.
- It was noted that the cells could be taken to a higher passage number to produce more cells for human use. However, the process that is used to produce cells for the animal studies should ideally be identical with respect to passage number, formulation, and final cell handling prior to administration. Thus, reviewers cautioned that scale up and passage number of cells may impact efficacy.
- The team should be very careful to make sure that these later passage cells are tested in pre-clinical animal studies and future development work if this is what will be used for clinical trials. The FDA notes that pre-clinical animal studies should be performed using the same cells and manufacturing process that will be used to produce cells for human use.
- There is no plan included for a large animal study to assess cell migration and surgical technique, which will inform the final decision on cell dose, including numbers of injections, spacing of injections, volume of injections.
- The team is encouraged to obtain more in vivo data to support that the cell source is indeed safe.
- The tumorigenicity studies should be undertaken in large animals. Reviewers were unclear regarding what role the titration studies play.
- Reviewers commented that six month studies in mice are not likely to be relevant to humans with slow growing neural cells.

Additional Comments

- Reviewers suggested the team think more clinically. For example, clinical surgical expertise is not included in the key personnel. This expertise should be involved in pre-clinical planning.
- The cryopreservation effects need to be understood better.
- The proposed timeline is aggressive but attainable.
- The contingency plans are adequate.

Public Review Summary
PA TRAN: Partnering Opportunity for Translational Research Projects

Application #	TRAN1-08561
Title	Personalized Cell Therapy for Diabetes
Translational Candidate (as written by the applicant)	Preclinical studies will develop patient specific stem cell-derived islets that secrete insulin & other islet hormones for regulation of blood sugar
Area of Impact (as written by the applicant)	Genetically matched stem cell derived islets could provide treatment for diabetes without the need for immunosuppression or implantable devices.
Mechanism of Action (as written by the applicant)	The stem cell-derived islets contain insulin-producing pancreatic β cells. These differentiated cells will be transplanted into patients who suffer from diabetes in order to replace the β cells that are missing or dysfunctional in the pancreatic islets of those patients. The stem cells used to generate these replacement islets will be genetically matched to the patient, enabling transplantation without long-term immunosuppression.
Unmet Medical Need (as written by the applicant)	Millions suffer from Type 1 & Type 2 diabetes, which significantly impact quality of life and lead to serious complications. This proposal develops an alternative therapy with potential to transform the lives of those patients. First target is patients with insulin dependent, non-autoimmune diabetes.
Project Objective (as written by the applicant)	Pre-IND meeting with the FDA
Major Proposed Activities (as written by the applicant)	• Production of the starting stem cell material from patients. • Optimize manufacturing of differentiated cell therapy product. • Preclinical safety and efficacy studies of the product.
Statement of Benefit to California (as written by the applicant)	Many CA citizens are impacted by diabetes, including particularly high numbers with non-autoimmune, insulin dependent diabetes. This translational research aims to bring academic discoveries from lab of Doug Melton to the clinic, through generation of patient specific stem cell derived islets for transplant. Success in this program could have have immediate benefit to the California patients involved and would also lead the way to a new cell therapy broadly applicable to people with diabetes.
Funds Requested	$5,000,000
GWG Recommendation	***Tier 1 – Exceptional merit and warrants funding, if funds are available.***

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.

Median	90
Standard Deviation	3
Highest	95
Lowest	85
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available.	14
Tier 2 (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?	13	0	1
Is the rationale sound?	12	0	2
Is the proposal well planned and designed?	13	0	1
Is the proposal feasible?	11	0	3

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 strong, well-designed, feasible, and high impact proposal.
- The proposal has excellent product development plans and great regulatory support.
- The proposal addresses an important area and is supported by a strong team.
- The plans for FDA approval seem logical.

- The plan is based on excellent science.
- The patient selection as part of development is a strong plus.

Concerns

- A concern with patient subject selection is whether this approach is generalizable. The target population should not be limited to a specific racial or ethnic group. Although individuals in that group may be more likely to meet inclusion criteria, inclusion criteria should be based on BMI (body mass index), evidence of beta cell failure, and lack of autoimmunity.
- Scale up could be a potential risk.

Additional Comments

- A more aggressive timeline would not be realistic. In fact, the proposed timeline doesn't provide for delay or the need to repeat steps.

Public Review Summary
PA TRAN: Partnering Opportunity for Translational Research Projects

Application #	TRAN1-08584
Title (as written by applicant)	Targeted nanotherapeutics to eradicate acute leukemia stem cells.
Translational Candidate (as written by applicant)	This project will develop nanoparticles that can specifically target and kill acute leukemia stem cells and decrease toxicity of chemotherapy.
Area of Impact (as written by applicant)	Nanoparticles developed in this project can target and kill leukemia stem cells that are usually resistant to conventional chemotherapy.
Mechanism of Action (as written by applicant)	Leukemia stem cells are a special group of leukemia cells that are resistant to conventional chemotherapy, can regenerate leukemia cells and cause leukemia recurrence. Nanopaticles developed in this project are coated with a molecule that can specifically target and eliminate leukemia stem cells and cure leukemia from the very root. In addition, these nanoparticles can decrease toxicity of chemotherapy.
Unmet Medical Need (as written by applicant)	The chemotherapy drugs used today to treat acute myeloid leukemia were developed in 1970s, and can cure less than 30% of patients (less than 10% for those older than 60%). Those drugs are highly toxic and many patients die from toxicity. In addition, there is no drug targeting stem cells.
Project Objective (as written by applicant)	The drug will be ready for a clinical trial.
Major Proposed Activities (as written by applicant)	• Develop a procedure and conduct a pilot production of the nanoparticles targeting leukemia stem cells. • Determine the dose and toxicity of the nanoparticles targeting leukemia stem cells. • Conduct toxicity studies of the nanoparticles that will guide a clinical trial in human patients.
Statement of Benefit to California (as written by applicant)	Acute myeloid leukemia (AML) is the most common cause of leukemia death. Even with highly toxic chemotherapy, over 70% of AML patients will die from this disease or treatment-related toxicity. This project aims to develop a therapeutic agent to eradicate leukemia at its root and decrease treatment-related toxicity and death. This project may have huge financial benefits to California by developing a new drug.
Funds Requested	$7,301,881
GWG Recommendation	***Tier 2 – Not recommended for funding.***

Final Score: 51

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.

Median	50
Standard Deviation	12
Highest	65
Lowest	20
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available.	0
Tier 2 (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?	4	10	1
Is the rationale sound?	0	13	2
Is the proposal well planned and designed?	0	13	2
Is the proposal feasible?	0	12	3

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 investigator provides several preliminary data on binding specificity, targeting capability, and treatment efficacy.

Concerns

- The drug development plan is inadequate.
- The preliminary data does not support proposal; data from the Principal Investigator's published paper seems to be missing or ignored in this proposal.

- The investigator does not provide sufficient justification on dosing schedule and treatment cycles.
- Several major inconsistencies are present. For example, the targeting data does not appear convincing. Also, there are missing controls in the experimental design.
- Potential off target effects of the nanoparticles are not suitably addressed.
- Humanized studies are not included.

Additional Comments

- No relevant comments were made by the reviewers.

Public Review Summary
PA TRAN: Partnering Opportunity for Translational Research Projects

Application #	TRAN1-08586
Title (as written by the applicant)	Selective inhibitor nanoparticles targeting liver cancer stem cells
Translational Candidate (as written by the applicant)	Selective inhibitor nanoparticles targeting liver cancer stem cells
Area of Impact (as written by the applicant)	Cure for late-stage metastatic hepatocellular carcinoma, cholangiocarcinoma and hepatoblastoma
Mechanism of Action (as written by the applicant)	The underlying hypothesis for our program is that comprehensive functional interrogation of CSCs results in the identification of novel CSC targets with broad applicability. Inhibition of these newly defined CSC pathways will reduce CSC content and thus prevent tumor relapse during/following treatment. Several rounds of screenings, i.e. biological replicates and using a large panel of tumors, aid to further consolidate the list of relevant targets.
Unmet Medical Need (as written by the applicant)	One goal of targeted cancer therapy is to eliminate all malignant tumor-initiating cells (TICs: namely 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.
Project Objective (as written by the applicant)	Readiness for transfer to manufacturing
Major Proposed Activities (as written by the applicant)	• Complete nonclinical safety studies. • Assess clinical safety of the therapeutic. • Manufacture product to supply the proposed trial.
Statement of Benefit to California (as written by the applicant)	The number of Californians have liver cirrhosis due to hepatitis C infection, alcoholic liver disease or cholestatic diseases. Because Hispanics have an increased risk of developing NASH and alcoholic liver diseases, California, the state with the largest Hispanic population in the US, will be impacted by this epidemic. Thus, developing liver cancer 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	$1,092,000
GWG Recommendation	***Tier 2 – Not recommended for funding.***

Final Score: 26

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.

Median	25
Standard Deviation	10
Highest	50
Lowest	15
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available.	0
Tier 2 (1-84): Not recommended for funding.	15

Score Influences Counts

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	10	3
Is the rationale sound?	1	11	3
Is the proposal well planned and designed?	1	11	3
Is the proposal feasible?	1	11	3

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

- No relevant comments were made by the GWG.

Concerns

- Reviewers expressed concerns regarding the poor presentation of the application. Among other problems, there is a deep lack of understanding of steps required to develop a product that could be approved by the FDA. For example, the development of a product containing previously approved drugs for a novel indication requires regulatory approval.
- The therapeutic candidate is poorly described. The team does not appear to understand the definition of a Target Product Profile.
- Reviewers found the goals of the proposed project difficult to understand. Whether the proposed project is to make nanoparticle-based drug therapy or to identify the targets and make therapeutic agents is not clear.
- The underlying rationale is presented in the form of assertions with minimal supporting evidence.
- The experimental design is poorly conceived.
- The project plan is overambitious. The plan purports to develop both a novel diagnostic and novel therapeutic formulation. Based on this application, the chances that the project team would bring either a diagnostic or therapeutic to pre-IND stage appear highly unlikely.
- No description of the nanoparticle production is presented.

Additional Comments

- It is unlikely the FDA will accept this proposal in its current form. The team should seek regulatory input on how to prepare experiments for an FDA submission.
- It seems like a project to test nanodelivery of a chemotherapy.

Public Review Summary
PA TRAN: Partnering Opportunity for Translational Research Projects

Application #	TRAN1-08635
Title (as written by applicant)	Placental Derived Natural Killer Cells to Target Solid Tumor Cancer Stem Cells (CSC)
Translational Candidate (as written by applicant)	Placental-derived stem cells becoming a unique NK-like cell
Area of Impact (as written by applicant)	Solid tissue cancers
Mechanism of Action (as written by applicant)	These expanded cells share many characteristics as NK cells but appear to represent a unique stage in differentiation and a cell-type with advantageous properties. These cells have been demonstrated to persist for much longer periods of time in vivo, exhibit broad anti-tumor effects and have a unique phenotype including sustained expression of the Fc receptor, CD16, which is lost on activated mature NK cells.
Unmet Medical Need (as written by applicant)	Cancer continues to lead as a major cause of mortality in the U.S., the vast majority of cancer patients will relapse and succumb to metastasis. This immunotherapeutic cell therapy in combination with conventional therapies may eradicate the CSC population and result in sustained anti-tumor effects.
Project Objective (as written by applicant)	Pre-IND
Major Proposed Activities (as written by applicant)	• Effects of placental derived stem cell NK cell on solid cancer cell killing & CSC phenotype in vitro. • Effects of placental-derived stem cell NK cell on solid cancer cell killing & CSC phenotype in vivo. • Effects of placental-derived stem cell NK cell on tumor growth & CSC elimination in xenograft models, and prepare and submit preIND package.
Statement of Benefit to California (as written by applicant)	Cancer continues to lead as a major cause of mortality in the U.S. With advanced disease despite use of extensive conventional cytoreductive cancer therapies, the vast majority of cancer patients will relapse and succumb to metastasis. This unique “off-the-shelf” immunotherapeutic cell therapy product of NK-like cells from placenta derived stem cells could then be used in combination with conventional cancer therapies to eradicate the CSC population and result in sustained anti-tumor effects.
Funds Requested	$2,368,818
GWG Recommendation	***Tier 1 – Exceptional merit and warrants funding, if funds are available.***

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.

Median	90
Standard Deviation	3
Highest	97
Lowest	85
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available.	15
Tier 2 (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	4
Is the rationale sound?	10	0	5
Is the proposal well planned and designed?	10	0	5
Is the proposal feasible?	10	0	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

- The proposal provides outstanding preliminary data and a good experimental plan.
- A great team is proposed to support the studies.
- The project is ready for translation.
- The proposal provides evidence of complementary activity with other treatment modalities.

Concerns

- Applicants need to address the potential for immune rejection of the off-the-shelf PiNK.

Additional Comments

- A trial is already underway for hematologic malignancies. The applicant might use these results to modify current experimental design.

Public Review Summary
PA TRAN: Partnering Opportunity for Translational Research Projects

Application #	TRAN1-08645
Title (as written by the applicant)	Human Embryonic Stem Cell-Derived Neural Stem Cells for Severe Spinal Cord Injury (SCI)
Translational Candidate (as written by the applicant)	Human neural stem cells derived from the H9 (WA09) embryonic stem cell line.
Area of Impact (as written by the applicant)	The targeted area of impact for the translational candidate is spinal cord injury.
Mechanism of Action (as written by the applicant)	We aim to build new connections across sites of spinal cord injury by grafting human neural stem cells (NSCs) directly into the lesion site. This is potentially a much more powerful treatment for spinal cord injury than other neural stem cell clinical trials currently in progress. Other approaches are attempting to improve the function of the small number of spared connections that are left in people after SCI, whereas our approach aims to build and restore many more connections.
Unmet Medical Need (as written by the applicant)	Currently, there is no effective treatment for spinal cord injury (SCI). We will implant neural stem cells (NSCs) into sites of severe SCI, to form new neuronal relays across the site of injury, reestablishing the ability of the brain to activate neural circuits below the lesion to improve function.
Project Objective (as written by the applicant)	Pre-IND meeting.
Major Proposed Activities (as written by the applicant)	• Manufacture and validate both MCBs and WCBs of the cGMP-grade developmental candidate: H9 (WA09) ESC-derived NSCs. • Short-term safety/toxicity studies of translational candidate in rodent and large animal models of spinal cord injury. • Long-term safety/toxicity studies of developmental candidate in rodent and large animal models of spinal cord injury.
Statement of Benefit to California (as written by the applicant)	The completion of this proposal would benefit California in three ways, by (1) improving the quality of life and decreasing the personal and financial burden of care for Californian patients living with spinal cord injury, (2) maintaining California's status as one of the foremost centers of translational stem cell research in the world, and (3) directly providing jobs to Californians.
Funds Requested	$5,603,017
GWG Recommendation	***Tier 2 – Not recommended for funding.***

Final Score: 49

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.

Median	50
Standard Deviation	9
Highest	65
Lowest	20
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available.	0
Tier 2 (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?	3	9	2
Is the rationale sound?	0	12	2
Is the proposal well planned and designed?	1	11	2
Is the proposal feasible?	0	12	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

- No relevant comments were made by the GWG.

Concerns

- The preliminary data do not support the proposal or moving forward with the candidate. Proof of concept data showing benefit with these cells that are proposed must be demonstrated, yet evidence of efficacy with human cells was not provided in the application,.
    - Evidence for in vivo efficacy of the product candidate human cell population is lacking, including lack of behavioral studies demonstrating efficacy.

- For preclinical animal studies, evidence that the candidate does not worsen the condition does not establish efficacy - this is not the appropriate benchmark.
- The applicant provides a very speculative explanation as to why there is no efficacy, failing to consider the possibility that they are using the wrong cell.

- The cell source is not consistent.
- The time line is inappropriately aggressive.

Additional Comments

- No relevant comments were made by the GWG.

Public Review Summary
PA TRAN: Partnering Opportunity for Translational Research Projects

Application #	TRAN2-08510
Title (as written by applicant)	MRI-based measurements of pH in spinal discs: A diagnostic tool for stem cell therapies
Translational Candidate (as written by applicant)	An MRI scan that can detect pH-level dependent low back pain.
Area of Impact (as written by applicant)	The candidate will be highly beneficial for the development of stem cell therapies for back pain.
Mechanism of Action (as written by applicant)	The MRI software will be able to diagnose which of the discs in the spine is the cause of pain. It will also enable the monitoring of disc healing after stem cell therapy.
Unmet Medical Need (as written by applicant)	To date there is no objective, quantitative, means to detect the origin of back pain and to monitor the effect of stem cells on treated discs. There is a need for a non-invasive diagnostic tool which will be able to detect painful discs.
Project Objective (as written by applicant)	Pre submission of 510(K) meeting with the FDA.
Major Proposed Activities (as written by applicant)	• Validate the sensitivity and specificity of the MRI software in a pig model of stem cell therapy to degenerate discs. • Establish clinical protocol for diagnosis and monitoring of disc regeneration following stem cell therapy.
Statement of Benefit to California (as written by applicant)	“My back hurts, Doc”. It’s one of the most common complaints heard by Californian family doctors. Traditional diagnosis of discogenic back pain includes invasive and painful procedure, discography. This study comes to replace this procedure with non-invasive imaging and promote future stem cell therapy for chronic back pain. Successful stem cell therapy will benefit all Californian residents by reducing workdays loos, medical costs and improving quality of life.
Funds Requested	$1,711,631
GWG Recommendation	***Tier 2 – Not recommended for funding.***

Final Score: 62

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.

Median	62
Standard Deviation	8
Highest	75
Lowest	50
Count	14

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available.	0
Tier 2 (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?	3	6	5
Is the rationale sound?	1	6	7
Is the proposal well planned and designed?	0	8	6
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

- Good technology and already funded by an RO-1 to get human data.
- pH as an indicator of anaerobic metabolism and lactic acidosis is a valid variable for non invasive testing, and MRI capability for this would be useful.

Concerns

- The software and MRI capability for pH measurement are useful to health care providers but a variable in an otherwise complex analysis.

- Multiple pathologic findings can be found with a low pH and thus does not justify a stem cell therapy.
- pH will change after stem cell administration.
- Back pain can arise from many different causes.
- Stem cell applications may or may not be advisable for all of these conditions; there is a need for mechanical solution in addition to a regenerative one.
- An incremental advancement at best from PI's NIH proposal.

Additional Comments

- A major issue is clinical relevance. A diagnostic that could do this noninvasively would address a huge medical need and the idea is great. However, the proposal relies on the assumption that a physician could identify which disc is affected in a patient with back pain, and it could create an incentive to apply stem cell therapy where it might not even be needed.

Public Review Summary
PA TRAN: Partnering Opportunity for Translational Research Projects

Application #	TRAN2-08615
Title (as written by the applicant)	PET imaging probes to monitor critical steps in stem cell-based therapies for liver failure in patients
Translational Candidate (as written by the applicant)	PET imaging probes that accumulate in healthy hepatocytes
Area of Impact (as written by the applicant)	There is a lack of sensitive and selective methods for understanding what happens to cell-based therapies once they are injected into patients.
Mechanism of Action (as written by the applicant)	Hepatocytes (derived ex vivo through reprogramming of other cells) and other cell-based therapies hold great promise to improve liver health. However, these therapies are complicated biological entities that need to be monitored carefully in patients. This is especially true early in the treatment when there are many possible outcomes. These PET imaging probes will provide critical information on these early steps and will enable physicians to better treat patients with these therapies.
Unmet Medical Need (as written by the applicant)	There are no sensitive and selective methods for monitoring cell-based therapies that treat liver failure. We propose to further develop new PET imaging probes for imaging and quantifying liver function with the goal of obtaining FDA approval for the use of these imaging probes in patients.
Project Objective (as written by the applicant)	Preparation of an IND to submit to the FDA.
Major Proposed Activities (as written by the applicant)	• Confirm that the PET imaging probes work in human cells. • Ensure that the PET imaging probes are not toxic. • Develop clinical protocols for the synthesis and use of these imaging probes.
Statement of Benefit to California (as written by the applicant)	Liver failure is a leading cause of death for Californians. CIRM funded researchers are developing technologies to (1) transform cells into hepatocytes and (2) improve liver health in order to assist patients in liver failure. These PET imaging probes would enable physicians to non-invasively visualize hepatocytes and hepatocyte function in vivo and would improve the chance of these technologies reaching the clinic.
Funds Requested	$1,843,200
Recommendation	***Tier 2 – Not recommended for funding.***

Final Score: 57

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.

Median	55
Standard Deviation	9
Highest	70
Lowest	40
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available.	0
Tier 2 (1-84): Not recommended for funding.	15

Score Influences Counts

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	9	3
Is the rationale sound?	2	9	4
Is the proposal well planned and designed?	3	7	5
Is the proposal feasible?	3	8	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 proposal includes a great team that has processed several other FDA approved probes.

Concerns

- There is a lack of preliminary data regarding effects of probes on stem cells.
- The data presented appears weak.
- Approach is not good for stem cell tracking.

- Approach is good for imaging liver but not stem cells.
- No data is presented on effect of probe on stem cell derived hepatocytes or the endothelium required to develop a blood supply to these engrafting cells.
- No evidence is provided on ability of probes to detect changes in liver cell mass following cell transplants.
- The team has no experience or collaborators in stem cells or hematology.
- This proposal is a poor fit for CIRM; it is a good product without a sound rationale and lacking feasibility for use with stem cells.

Additional Comments

- Proposal seems like a solution looking for a problem.

Public Review Summary
PA TRAN: Partnering Opportunity for Translational Research Projects

Application #	TRAN3-08516
Title (as written by the applicant)	Improved bone repair by combining Reamer Irrigator Aspirator (RIA) bone graft with stem and progenitor cells recovered from the RIA effluent by SynGenX-LAB and associated equipment.
Translational Candidate (as written by the applicant)	System for recovering and anticoagulating stem and progenitor cells from RIA effluent intraoperatively using the SynGenX-LAB system.
Area of Impact (as written by the applicant)	The system will improve the effectiveness of bone grafts to repair large segmental defects or other clinical situations requiring bone grafts.
Mechanism of Action (as written by the applicant)	The system will add anticoagulant to assure that stem cells and progenitor cells harvested from the RIA effluent will remain viable in the bone graft. These cells, which are normally discarded as medical waste, will be added to the RIA graft in order to improve bone healing in complex nonunions and segmental defects.
Unmet Medical Need (as written by the applicant)	The augmented RIA graft will address the need for more reliable, rapid bone healing in patients who suffer from complex nonunions and other conditions requiring a bone graft. The proposed solution is safer and more cost effective than existing treatment methods.
Project Objective (as written by the applicant)	A pre submission meeting with the FDA.
Major Proposed Activities (as written by the applicant)	• Developing anticoagulant addition, and adapting the SynGenX-LAB system to process the RIA effluent. • Test SynGenX®-LAB in a large animal model of RIA-mediated bone repair. • Prepare for submission to the FDA, and pre-510K meeting to address potential issues.
Statement of Benefit to California (as written by the applicant)	The proposed research will contribute to California's reputation as a global leader in regenerative medicine. The research is translatable and clinically relevant. Funding of this research will increase the likelihood and speed of bringing the proposed therapy into clinical application, which will benefit many patients in California as well as other patients who may travel to California for treatment.
Funds Requested	$1,515,542
GWG Recommendation	***Tier 2 – Not recommended for funding.***

Final Score: 67

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.

Median	70
Standard Deviation	15
Highest	75
Lowest	20
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available.	0
Tier 2 (1-84): Not recommended for funding at this time	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?	4	9	2
Is the rationale sound?	2	5	8
Is the proposal well planned and designed?	1	8	6
Is the proposal feasible?	2	3	10

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 confidence that the device will work and provide value.
- The team is excellent.

Concerns

- The applicant did not provide suitable safety data and sterility information. Although it is a closed system, sterility, endotoxins, or mycoplasma testing needs to be addressed.

- There are inadequate measurements of efficacy provided. Robust preliminary data demonstrating efficacy should have been provided.
- The stem cell mix remains heterogeneous. Reviewers expressed reservations about giving mixed bone marrow mononuclear cell fractions.
- The dose needs to be identified and standardized. An uncharacterized and non-standardized product makes it difficult to determine if there is no effect. Currently, there is too much variability in the reamed material to understand if this approach is beneficial or not.
- The patient population needs to be better standardized.
- In particular, methodical testing of the reamed material is not well described.

Additional Comments

- A scaffold would benefit the proposed product.

Public Review Summary
PA TRAN: Partnering Opportunity for Translational Research Projects

Application #	TRAN3-08555
Title (as written by applicant)	Novel Device for Stem Cell Delivery into Brain Tumors
Translational Candidate (as written by 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 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 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 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 applicant)	Pre-IDE meeting
Major Proposed Activities (as written by applicant)	• IDE Design Phase
Statement of Benefit to California (as written by 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	$2,152,041
GWG Recommendation	***Tier 2 – Not recommended for funding.***

Final Score: 51

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.

Median	50
Standard Deviation	17
Highest	75
Lowest	20
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available.	0
Tier 2 (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	6	6
Is the rationale sound?	0	10	5
Is the proposal well planned and designed?	0	11	4
Is the proposal feasible?	0	9	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

- The proposal addresses a significant unmet need.

Concerns

- Reviewers expressed significant concern regarding the rationale for the treatment. Drilling and curing a part of glioblastoma is not the way to treat a patient with brain cancer. Infused cells may not find their way into the most distal invasive cells.

- Questions exist regarding the viability of transplanted cells in the microenvironment created by the device. Will the cells survive in the tumor for any length of time to exert an effect? The cell microenvironment may include a detrimental cytokine storm which may limit efficacy of cell therapy.
- No animal model for testing. Canine models of glioblastoma exist.
- The device, which may remove the tumor, needs material testing and testing in an appropriate animal model.
- This procedure cannot be done more than once. How will the efficacy be monitored for cell viability?
- There are concerns about the size of the team, applicant, and the capacity to complete the proposal.
- The administration of steroids is likely to kill the infused T cells.

Additional Comments

- It was suggested that a canine model of glioblastoma should be considered as a path forward.

Public Review Summary
PA TRAN: Partnering Opportunity for Translational Research Projects

Application #	TRAN3-08574
Title (as written by the applicant)	Enhanced Engraftment of Transplanted Stem Cells using Growth Factor Sequestering Hydrogels
Translational Candidate (as written by the applicant)	Bioinspired hydrogel to improve transplanted donor cell engraftment to treat tissue ischemia.
Area of Impact (as written by the applicant)	A major bottleneck in various disease treatments is the lack of engraftment of the transplanted donor cells. Our device will alleviate this problem.
Mechanism of Action (as written by the applicant)	Matrix-Assisted Cell Transplantation – A major bottleneck in various disease treatments is the lack of survival and engraftment of the transplanted stem cells. We propose an advanced biomaterial, as a medical device, to efficiently promote transplanted cell survival, engraftment, and their contribution to improvement in tissue function. This proposal will optimize specialized advanced biomaterials to improve the treatment of ischemic disease.
Unmet Medical Need (as written by the applicant)	After stem cell transplantation into various tissues, donor cell death occurs within a few days due to ischemia and lack of nutrients. We have developed a novel system that combines differentiated stem cells and hydrogel networks that embody critical matrix features that alleviate this problem.
Project Objective (as written by the applicant)	IDE-enabling preclinical and manufacturing plans.
Major Proposed Activities (as written by the applicant)	• Optimize biomaterial prototypes and verify their biocompatibility (non-clinical safety). • Assess pre-clinical safety and efficacy of the biomaterial in a limb ischemia model. • Develop manufacturing and IDE-enabling preclinical plans.
Statement of Benefit to California (as written by the applicant)	Tens of thousands of Californians suffer from diseases with outcomes of limb ischemia. Although CIRM-funded researchers are currently developing stem cell therapies to provide effective treatment, donor cell death occurs within a few days after transplantation due to ischemia, preventing cell engraftment and long-term clinical treatment. Our bioinspired material, combined with special stem cells, may greatly improve treatment outcomes, saving California taxpayers millions of dollars annually.
Funds Requested	$2,448,988
GWG Recommendation	***Tier 2 – Not recommended for funding.***

Final Score: 52

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.

Median	50
Standard Deviation	17
Highest	75
Lowest	1
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available.	0
Tier 2 (1-84): Not recommended for funding.	15

Score Influences Counts

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?	1	10	4
Is the rationale sound?	1	11	3
Is the proposal well planned and designed?	0	10	5
Is the proposal feasible?	0	11	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 safety and biocompatibility testing is excellent.

Concerns

- The translational path is wrong and significantly diminishes enthusiasm.
- This is not a medical device; thus, the proposed regulatory path is flawed. This appears to be a combination product or, at minimum, a biologic product.

- This proposed product is too complex. Every interaction of cell, gel, peptides, heparin, etc need to be tested.
- There are clear problems with the suitability of the proposed animal models. It is unclear if the proposed mouse model will yield sufficient data. A large animal model may be a better choice.
- The numbers proposed for the mouse studies do not add up if the team intends to use some animals for intermediate testing.
- The innovation is minimal regarding the hydrogel development.
- It is unclear if cardiac progenitor cells are the right cell choice for this proposal. This application to limb ischemia is not well tested.

Additional Comments

- No relevant comments were made by the reviewers.

Public Review Summary
PA TRAN: Partnering Opportunity for Translational Research Projects

Application #	TRAN4-08479
Title (as written by the applicant)	Integration defective lentiviral vector-mediated gene editing in human pluripotent stem cells
Translational Candidate (as written by the applicant)	The study proposes to develop a highly efficient tool for genetic modification of the human stem cell genome for basic research and clinical application.
Area of Impact (as written by the applicant)	The efficiency for genetic manipulation of human stem cells is low. The proposed strategy overcomes this barrier and expands stem cell application.
Mechanism of Action (as written by the applicant)	The proposed study meets the need for carrying out site-specific gene modification efficiently and reliably in the expanded repertoire of human ESCs and iPSC lines. The tool facilitates more efficient gene correction in human stem cells important for cell replacement therapies. It also has a major impact on the establishment of human disease models "in a dish". The tool's ability to mark lineage-specific genes will benefit the process of drug screening as well.
Unmet Medical Need (as written by the applicant)	In the era of personal medicine, such as the use of iPSCs in cell replacement therapies, an efficient and reliable strategy to genetically modify patient's iPSCs is critical. The proposed tool meets these requirements and can speed up the clinical application of iPSCs.
Project Objective (as written by the applicant)	Tool optimization for human stem cell application
Major Proposed Activities (as written by the applicant)	• Optimize the conditions of applying the tool in site-specific gene modification in human ESCs and iPSCs. • Apply the tool in gene correction in human iPSCs and gene tagging in human ESCs based on the optimized conditions determined in Activity 1.
Statement of Benefit to California (as written by the applicant)	The mission of CIRM is to support stem cell research for the discovery of cures, diagnostics and new research technologies. To fulfill these promises, it is frequently necessary to manipulate human stem cell genome. The tool developed by this proposal meets the need of an efficient and reliable technique for stem cell gene modification. To optimize the conditions for applying the tool would benefit California in disease treatment, drug screening and basic research in disease modeling.
Funds Requested	$1,282,458
GWG Recommendation	***Tier 2 – Not recommended for funding.***

Final Score: 79

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.

Median	80
Standard Deviation	2
Highest	80
Lowest	75
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available.	0
Tier 2 (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	2	6
Is the rationale sound?	5	1	9
Is the proposal well planned and designed?	0	7	8
Is the proposal feasible?	3	2	10

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 are promising initial results.
- This is an experienced and outstanding team.
- There is a great preliminary data set.
- There is significant economic impact for "disease-in-a-dish" technology advancement.

Concerns

- This is too early stage for translation.
- While proposing lots of good science, the specific aims are too diffuse to achieve the PA objective of translation of a tool. Focusing the aims on translating the proposed tool would increase enthusiasm.
    - Aim 1 is appropriate for a translational "tool" grant.
    - Aim 2 actually detracts from the application. It focuses too deeply on specific research projects of interest to the applicants. A revised application with expansion of Aim 1 and elimination of Aim 2 (except as is truly essential for technological proof-of-concept) would make this significantly stronger as a translational program.
    - Sub-Aim 1.6 is vague and confusing. It is better to focus on a true milestone rather than asking such an open-ended question about mechanism. Overall, this contributes to the sense that this a hybrid of a basic science and a translational application. Focusing on the tool aspect would strengthen the proposal for this particular funding mechanism.
- This application would benefit from clearer quantitative & qualitative targets for the optimization sub-milestones 1.1-1.5 and potentially more rigorous analysis (e.g., more emphasis on deep sequencing) to evaluate off-target effects.
- The applicant needs to define clear go/no-go criteria and standards that should be met to potentially make this technology a key component of the rapidly evolving field of gene editing, particularly for pluripotent human stem cells.
- The investigation of off target effects is not well-described and this issue needs to be investigated to determine the impact relative to current methods.
    - The applicant needs to assess off-target consequences. For example, is the better correction efficiency accompanied by more problems?
    - What is the off-target toxicity?
- The GFP project is less relevant to CIRM goals.
- This is not a breakthrough; other similar technologies are available and this proposal represents incremental progress.
- Is the tool going to be ready for translation?
- Is this the best group to develop the tool?

Additional Comments

- Consultant(s) with commercial product development experience could help.

Public Review Summary
PA TRAN: Partnering Opportunity for Translational Research Projects

Application #	TRAN4-08518
Title (as written by the applicant)	High throughput and high purity cell isolation for cell therapy development and production
Translational Candidate (as written by the applicant)	A Pre-Enrichment Tool (PET) for the isolation of stem cells and other targeted cells with higher purity and throughput than existing methods
Area of Impact (as written by the applicant)	Isolation of stem cells and other cells to >98% purity using sample volumes up to a billion cells at speeds up to 10 times faster
Mechanism of Action (as written by the applicant)	The pre-enrichment tool uses i)a magnetic separator that depletes unwanted sample using magnetic antibodies, ii) an acoustic focusing chip that concentrates large cells in the center of the flow stream, directs small cells, particles and debris to waste, and concentrates of cells of interest, and iii) direct fluid integration with FACS sorters. PET output is a sample with an increased concentration of target cells, improved cell spacing, and reduced background that is optimal for FACS sorting.
Unmet Medical Need (as written by the applicant)	Stem workflows often require the isolation of target cells that become the basis for subsequent analysis or a production process. Existing tools demand a tradeoff between sample purity and the speed at which the sample can be processed. The PET provides both high purity levels and high throughput.
Project Objective (as written by the applicant)	Beta prototypes for stem cell therapy developers
Major Proposed Activities (as written by the applicant)	• Design and development of sub-systems: i) control system ii) communication with FACS sorters iii) fluidics. • Integration of sub-systems, design for ease-of-use and manufacturability, quality control and characterization. • Beta testing in key workflows, in collaboration with stem cell researchers and cell therapy developers with subsequent improvements to the design.
Statement of Benefit to California (as written by the applicant)	The PET will provide more powerful capabilities to the stem cell community in California. As the project will be done in San Jose and may result in a product that is manufactured in California and commercialized globally, there is an economic multiplier effect. The PET will help ensure that pioneering stem cell therapies are developed in California and that it continues to be a world leader in the field thereby creating jobs and new high-impact therapies for Californians.
Funds Requested	$1,286,185
GWG Recommendation	***Tier 2 – Not recommended for funding.***

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.

Median	75
Standard Deviation	2
Highest	80
Lowest	70
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available.	0
Tier 2 (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?	4	4	7
Is the rationale sound?	3	3	9
Is the proposal well planned and designed?	2	2	11
Is the proposal feasible?	6	0	9

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 tool is useful.
- The applicant is highly expert in instrument design.

Concerns

- Proposal is not sufficiently impactful.
- It does not impact on a stem cell therapy bottleneck.

- It is unclear that this is a stem cell based technology.
- Reagent development is required to process cells and enrich cells; such reagents are not identified and it is unclear how soon this would be translated.
- Applicants need to address availability of clinical reagents necessary for therapeutic production.
- Is not clear why this approach is better than other enrichment approaches.
- Targeting via negative enrichment is costly, whereas positive selection is cleaner. Also, large scale up may not be possible.

Public Review Summary
PA TRAN: Partnering Opportunity for Translational Research Projects

Application #	TRAN4-08534
Title (as written by the applicant)	Real-time monitoring of stem cell differentiation for quality assurance in regenerative medicine applications
Translational Candidate (as written by the applicant)	A tool that can be used for quality assurance of all stem cell-derived treatments
Area of Impact (as written by the applicant)	A critical bottleneck for stem cell-based therapies is the concern for tumor formation after transplantation. This tool can identify dangerous cells.
Mechanism of Action (as written by the applicant)	Stem cells exhibit specific morphologic and dynamic characteristics when they differentiate into the cell types destined for treatments. These characteristics can predict cell fate, differentiation behavior, and ultimately, safety after transplantation. A spatial map of the cells can be generated from these data. Moreover, this map can be used to guide laser microdissection instruments to isolate cells to correlate with biochemical parameters, cell fate, and performance after transplant.
Unmet Medical Need (as written by the applicant)	Currently there is no standard quality assurance method to ensure safety of a stem cell based therapy. Traditional methods sample a small portion of the cells, but not the actual cells used for transplantation. Our tool can be used for real-time quality assurance thus filling an unmet need.
Project Objective (as written by the applicant)	Readiness for commercialization of our tool.
Major Proposed Activities (as written by the applicant)	• Design and build prototype hardware. • Design and test software algorithms that are specific to stem cell type and cell types that are derived from these stem cells. • confirm tool cell detection capabilities with traditional genetic and biochemical tests and correlate these with performance in rodents.
Statement of Benefit to California (as written by the applicant)	A critical bottleneck in bringing stem cell therapy to clinical applications is the concern for tumor formation after transplantation. This may be due to stem cell impurities or formation of cancer cells during manufacturing. Our tool can detect these unwanted cells during the manufacturing process. Ultimately, this tool can be used for quality assurance of all stem cell therapies to predict safety and effectiveness. This tool could help Californians receive safe and effective treatments.
Funds Requested	$1,583,760
GWG Recommendation	***Tier 2 – Not recommended for funding.***

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.

Median	70
Standard Deviation	7
Highest	85
Lowest	65
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available.	3
Tier 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	1	6
Is the rationale sound?	4	4	7
Is the proposal well planned and designed?	5	6	4
Is the proposal feasible?	2	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

- The rationale is strong.
- This is an important problem, and there is potential for impact.
- The proposed technology is interesting. This is good proposal with lots of upside.
- This is a strong team.

Concerns

- There are concerns about the ability to actually perform at clinical scale.
- The laser microdissection development is a distraction from main focus on ID of residual PSC.
- The specifications for success need to be higher (<1 PSC/million cells).
- The applicant needs to address the scale needed for clinical cell numbers (>1 billion cells).
- The applicant needs to provide additional data on software development and algorithms used.
- The applicant indicates NIST, which has very advanced technology on this topic, is involved, but no personnel are named. Therefore, it is not certain to what degree this highly accomplished expertise is involved in the project.
- Some specifics of development are left out, leaving the reviewer not able to gauge exactly what will be done.
- The application for laser dissection is not well described.
- There are concerns regarding the overall feasibility of the proposal.

Additional Comments

- No relevant comments were made by the GWG.

Public Review Summary
PA TRAN: Partnering Opportunity for Translational Research Projects

Application #	TRAN4-08567
Title (as written by applicant)	High-resolution, High-Sensitivity, Quantitative, and Functional *in vivo* Stem Cell Imaging Using Magnetic Particle Imaging
Translational Candidate (as written by applicant)	Development of Magnetic Particle Imaging for tracking the *in vivo* localization, viability, and clearance of a variety of cell therapy candidates.
Area of Impact (as written by applicant)	Although robust *in vivo* imaging is critical for developing clinical cell therapies, we lack a robust, quantitative, longitudinal cell tracking method.
Mechanism of Action (as written by applicant)	MPI tracks cell-based therapies over months with unprecedented image contrast, resolution, quantitativeness, and soon *in vivo* monitoring of cell viability. Because MPI directly detects iron oxides, it boasts superb image specificity for labeled cells. We have identified a way to improve MPI image resolution by 10-fold to 120 um and detection sensitivity by 40-fold to 20 cells. These innovations will facilitate monitoring the fate of cell therapy candidates in the development pipeline.
Unmet Medical Need (as written by applicant)	The clinical translation of cell therapy candidates has been hindered by the lack of accurate monitoring techniques to ensure safety and efficacy. By monitoring the location, number, and viability of cell grafts, MPI enables researchers and clinicians to accelerate translation of cell therapies.
Project Objective (as written by applicant)	20μm 3D MPI imager for preclinical cell tracking
Major Proposed Activities (as written by applicant)	• Develop MPI scanning software and hardware for 10-fold resolution boost, 40-fold sensitivity boost, and relaxation-based image contrast. • Tracer development for high-resolution MPI cell tracking and relaxation-based viability imaging. • Discrete MPI demonstration for 19F MRI comparison, cell viability imaging and neural graft migration monitoring.
Statement of Benefit to California (as written by applicant)	The development of stem cell-based therapies for cardiovascular disease, diabetes, stroke, Parkinson's, and Alzheimer's would greatly improve health outcomes for Californian families and reduce state healthcare costs. Unfortunately, we now lack an acceptable method to track such therapies, making it difficult to assess their safety and efficacy. Our proposed method, called Magnetic Particle Imaging, offers a safe and effective way to track cell therapies quantitatively over months in the body.
Funds Requested	$1,449,817
GWG Recommendation	***Tier 2 – Not recommended for funding.***

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.

Median	70
Standard Deviation	4
Highest	75
Lowest	60
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available.	0
Tier 2 (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?	1	10	4
Is the rationale sound?	2	8	5
Is the proposal well planned and designed?	2	7	6
Is the proposal feasible?	4	5	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

- This is a very strong team.
- The proposed technology is interesting.

Concerns

- It is difficult to see how this would impact the development of stem cell therapies or impact patient outcomes. When compared to nuclear medicine, the technique will not enhance clinical translation.

- The advantages of the approach are overstated when compared to genetic markers.
- Reviewers expressed concerns regarding the specificity of labeling, cell survival, and the spreading of the label.
- The labeling rationale is poor. As cells divide, the label will dilute and cells may no longer be visible. Also, there is no ability to discriminate between cells labeled before injection and cells that die and for which particles are taken up by macrophages.
- Superparamagentic iron oxide (SPIO) nanoparticles are unlikely to pass through the FDA.
- This large SPIO may not be useful to label HSC.

Additional Comments

- No relevant comments were discussed.

Public Review Summary
PA TRAN: Partnering Opportunity for Translational Research Projects

Application #	TRAN4-08575
Title (as written by the applicant)	A Tool to Quantitate Antigen-Specific T cell populations for Engineered Stem Cell Cancer Immunotherapies
Translational Candidate (as written by the applicant)	A tool understanding, at a molecular level, what T cell populations can be most effectively harnessed for cancer immunotherapies
Area of Impact (as written by the applicant)	The Tool can help define cancer vaccines for promoting strong immunotherapy responses in larger cancer patient populations
Mechanism of Action (as written by the applicant)	The tool is designed to resolve the specific molecular interactions that can lead to a successful patient outcome during a cancer immunotherapy treatment. Those specific molecular interactions, once identified, can also be harnessed as a vaccine for promoting stronger patient responses to immunotherapies, including recently emerging approaches to cancer immunotherapy via stem cell engineering.
Unmet Medical Need (as written by the applicant)	The specific molecular interactions between T cells and tumor cells can vary from patient to patient. Existing tools resolve only a fraction of a percent of those interactions. The proposed tool has the potential to resolve the majority of those interactions.
Project Objective (as written by the applicant)	Identify neoantigens for improving immunotherapies
Major Proposed Activities (as written by the applicant)	• Extend to tool cover a larger fraction of the patient population. • Modify tool to permit molecular identification of what in the tumor draws T cells, and the genetic nature of those T cells. • Demonstrate that analysis with the tool can be done through blood, rather than requiring a biopsy, so as to easily follow stem cell immunotherapies.
Statement of Benefit to California (as written by the applicant)	Cancer immunotherapy is a revolutionary advance in cancer therapy - it is not just a treatment, but a potential cure. Several CA scientists and physicians are leaders, and CA patients are benefiting from these advances. Many patients, however, do not respond to existing immunotherapies. A new idea is to engineer an anti-tumor response into patients at the stem cell level. That type of approach will likely eventually require an accompanying vaccine. This tool helps define that vaccine.
Funds Requested	$1,037,632
GWG Recommendation	***Tier 2 – Not recommended for funding.***

Final Score: 62

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.

Median	60
Standard Deviation	7
Highest	78
Lowest	50
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available.	0
Tier 2 (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	4
Is the rationale sound?	2	9	4
Is the proposal well planned and designed?	0	11	4
Is the proposal feasible?	0	11	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 Principal Investigator (PI) is highly experienced and has an outstanding record of productivity.

Concerns

- It is questionable that this proposal will have any impact in stem cells based vaccines or T-cell therapy.
- The proposed tool is too complex to be translatable. For example, the proposed separation to individual T cells for sequencing is highly technical and fraught with feasibility issues.
- The development plan may not be feasible within the proposed time period.

- The regulatory strategy is not well-defined.
- Even if objectives are achieved, *in silico* predictions may not be valid/successful for vaccine development.

Additional Comments

- No relevant comments were made.

Public Review Summary
PA TRAN: Partnering Opportunity for Translational Research Projects

Application #	TRAN4-08598
Title (as written by the applicant)	Microelectrophysiological Assessment of Pharmacology using Labchip Electroencephalogram (MAPLE) for neurological diseases
Translational Candidate (as written by the applicant)	A culture system that allows real-time analysis of electrophysiology of neurons derived from iPSC-generated NSCs.
Area of Impact (as written by the applicant)	The platform will provide a high-throughput and reliable pharmacological output for screening seizure-related drugs for patient-specific therapy.
Mechanism of Action (as written by the applicant)	The electrophysiological functional assay using the MAPLE system could be used as a patient surrogate, allowing the evaluation of different drug dosages, protecting the patient from the usual drug odyssey. In other words, one could screen a patient's cells with a variety of drugs known to be useful for seizures, for example, to more quickly arrive at the best drug or combination of drugs for that particular patient's seizures.
Unmet Medical Need (as written by the applicant)	Finding the appropriate drug regimen to treat seizure disorders is quite time-consuming. Clinicians generally prescribe one medication and evaluate its effectiveness over weeks or months. Thus, there can be a journey of many months before a proper drug cocktail for a given patient can be devised.
Project Objective (as written by the applicant)	Readiness for transfer to manufacturing.
Major Proposed Activities (as written by the applicant)	• Design and develop the MAPLE chip and system. • Develop bioassay protocols for the MAPLE system. • Validate the MAPLE system using specific patient derived samples.
Statement of Benefit to California (as written by the applicant)	Currently, a patient's seizures tend to be controlled with multiple, rather than single, drugs. Finding the right drug combination is educated trial and error and can take many months. Our MAPLE device, using the patient's own cells, will allow us to quickly arrive at the proper drug combination without subjecting the patient to lengthy trial and error drug exposures.
Funds Requested	$1,204,432
GWG Recommendation	***Tier 2 – Not recommended for funding.***

Final Score: 73

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.

Median	75
Standard Deviation	8
Highest	85
Lowest	55
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available.	1
Tier 2 (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?	9	2	4
Is the rationale sound?	6	6	3
Is the proposal well planned and designed?	3	9	3
Is the proposal feasible?	1	6	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

- Reviewers agreed this proposal contains a promising idea and the end product has a strong value proposition.
- The risk profile is appropriate.

Concerns

- The enthusiasm is critically dampened by the shortcomings described below:
  - Data showing that the seizing patients have a predictable pattern in EP and response that matches the phenotype.

- Data gained with the use of already established cell lines.
- Data showing only one patient with one drug is presented. More robust studies to correlate with available patient findings are necessary.
- Retrospective predictability is not presented.

- In particular, reviewers emphasized that the team does not show that there are significant electrophysiological differences among iPSC-derived neuronal populations from different donor individuals that in any way correlate with whether these donors are subject to seizures. A "disease in a dish" model needs a clear relationship between an *in vitro* and disease phenotype. Thus, the absence of data in the application supporting the rationale leads to the lower score.
- The correct proof of concept experiments need to be performed to show that the read out is predictive of an effective or failed treatment.
- There is difficulty finding convincing data to demonstrate specificity or selectivity of the test.
- This project as it is currently proposed will move slowly to translation.

Additional Comments

- The proposal must incorporate suitable normal patient control(s) to see if the disease is valid. There is difficulty discerning the difference between the disease and normal phenotype.
- The engineering is ahead of the biology.
- This application is more appropriate for an earlier stage of funding, such as CIRM's Quest (DISC 2) Program. An earlier stage of funding would permit the team the gain the necessary missing preliminary data and create a stronger proof of concept.

Public Review Summary
PA TRAN: Partnering Opportunity for Translational Research Projects

Application #	TRAN4-08607
Title (as written by the applicant)	In situ forming hydrogels for effective stem cell delivery and engraftment after stroke
Translational Candidate (as written by the applicant)	A gel-like material will be studied as a protective environment for transplanted cells
Area of Impact (as written by the applicant)	Brain repair after stroke through improving stem cell engraftment with the healthy brain
Mechanism of Action (as written by the applicant)	The goal is to engineer cells ex vivo that can replace the lost cells in the brain after stroke. Our tool will facilitate the engraftment of the transplanted cells with the healthy brain by providing them with a protected environment within the harsh stroke environment until the environment is more hospitable.
Unmet Medical Need (as written by the applicant)	There is no current treatment for stroke past the initial hours. Thus stroke is the leading cause of adult disability in the US.
Project Objective (as written by the applicant)	Available for wide use
Major Proposed Activities (as written by the applicant)	• We will encapsulate the cells within the protective hydrogel material that also promotes their differentiation to active neurons. • The injected cells will then be implanted into the stroke cavity to promote repair. • Cell viability and functional engraftment will be assed.
Statement of Benefit to California (as written by the applicant)	Stem cell therapy has the potential to improve the life of many patients. However, delivery of the cells to their target site has been a bottleneck to their translation. This proposal aims to develop a tool for the effective transplantation of stem cells. Though we will use stroke as our disease target, the proposed tool could be used for stem cell deliver to a variety of other diseases.
Funds Requested	$1,519,920
GWG Recommendation	***Tier 2 – Not recommended for funding.***

Final Score: 59

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.

Median	60
Standard Deviation	9
Highest	75
Lowest	50
Count	15

Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available.	0
Tier 2 (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?	1	9	5
Is the rationale sound?	1	7	7
Is the proposal well planned and designed?	1	9	5
Is the proposal feasible?	1	8	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

- No relevant comments were made by the reviewers.

Concerns

- This project is not ready for the translational path. It is premature for this program and there are weaknesses in the biology.
- This proposal is in a very crowded field: gels for stroke. Insufficient data are provided to determine the value of this candidate relative to other gels under development.

- There are no POC data that demonstrate any functional benefit as a stroke treatment. Also, there is no timeline to administer cells into the stroke area. There will be limited window for treatment feasibility. These data should be demonstrated, and then optimization may occur.
- In addition, preliminary data regarding chronic injury application are not suitably discussed.
- Injection into the brain has a finite space which precludes injection of large volumes. This issue needs to be addressed.
- A suitable neuro-clinician is missing.
- The clinical target is a poor choice.

Additional Comments

- No relevant comments were made by the reviewers.