TRAN AWARDS 10/31/19

$10,946,695 GWG RECOMMENDED

TBD AMOUNT AVAILABLE

$0 BOARD APPROVED

							Score Range		Number of GWG Votes						
APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Resubmission	Previous CIRM Funding	Disease Indication	Product Type	Approach
TRAN1-11536	Ex Vivo Gene Editing of Human Hematopoietic Stem Cells for the Treatment of X-Linked Hyper-IgM Syndrome	$4,896,628	Y	92	92	3	85	95	15	0	N	Y	Hyper-IgM syndrome	Cell and gene therapy	Autologous hematopoietic stem cell ex vivo gene correction for transplant
TRAN1-11555	BCMA/CS1 Bispecific CAR-T Cell Therapy to Prevent Antigen Escape in Multiple Myeloma	$3,176,805	Y	85	83	5	65	88	10	5	N	N	Multiple myeloma	Cell and gene therapy	Bispecific CAR-T cells targeting BCMA and CS1 in multiple myeloma cells
TRAN1-11544	Neural Stem cell-mediated oncolytic immunotherapy for ovarian cancer	$2,873,262	Y	85	83	6	70	90	9	6	N	Y	Ovarian cancer	Cell therapy	Allogeneic neural stem cells to target ovarian cancer and deliver oncolytic virus
TRAN1-11611	Development of a human stem cell-derived inhibitory neuron therapeutic for the treatment of chronic focal epilepsy	$5,246,287	N	78	76	6	60	84	0	15	N	Y	Epilepsy	Cell therapy	Allogeneic hESC-derived inhibitory neural cells for transplant into seizure focal area of brain

Application #	TRAN1-11536
Title (as written by the applicant)	Ex Vivo Gene Editing of Human Hematopoietic Stem Cells for the Treatment of X-Linked Hyper-IgM Syndrome
Translational Candidate (as written by the applicant)	Human hematopoietic stem cells that have been gene-corrected at the CD40L gene to treat patients with X-Linked Hyper-IgM Syndrome
Area of Impact (as written by the applicant)	These studies will bring stem cell gene therapy for XHIM closer to the clinic, especially those without an HLA match or infections too severe for HSCT.
Mechanism of Action (as written by the applicant)	The CRISPR/Cas9 platform allows site-specific integration of a corrective copy of the CD40L gene at its normal location, maintaining expression of the corrective DNA under control of natural regulatory elements. Transplantation of gene-corrected hematopoietic stem cells, which are self-renewing and long-lived, produces all blood lineages, including T lymphocytes with restored CD40L expression than can stimulate B cells to produce class-switched immunoglobulin.
Unmet Medical Need (as written by the applicant)	There is no curative treatment for XHIM patients without a bone marrow match or with severe infections. Gene corrected HSC can cure XHIM and provides a therapeutic option for these patients. This proposal will advance the field of stem cell gene therapy and treatment of primary immunodeficiencies.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	• Characterize clinical grade critical reagents in healthy and XHIM hematopoietic stem cells. Perform clinical scale run and pilot toxicology study. • Assess off-target insertions and deletions caused by CRISPR/Cas9 in additional cell lines and in primary hematopoietic stem cells. • Prepare clinical protocol, investigator's brochure, consent forms, and Pre-IND package. Complete Pre-IND meeting with the FDA.
Statement of Benefit to California (as written by the applicant)	Safe, definitive therapies for XHIM represent an unmet medical need. Allogeneic stem cell transplant is frequently complicated by graft-versus-host disease and worsening of pre-existing infections. Successful demonstration that stem cell gene therapy can safely and effectively cure XHIM will shift the paradigm by which patients will be treated, led by California's position as a leader in the field of gene therapy. This will result in improved patient care in the state and around the world.
Funds Requested	$4,896,628
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

SCORING DATA

Final Score: 92

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

Mean	92
Median	92
Standard Deviation	3
Highest	95
Lowest	85
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	15
(1-84): Not recommended for funding	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific members of the GWG were asked to

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 15	• The proposed product will fulfill an unmet medical need. • X-linked Hyper-IgM Syndrome is very rare, and is currently treated by bone marrow transplant. If the proposed therapy works, it would eliminate issues associated with bone transplantation. • This potentially curative strategy matches the CIRM mission and is not likely to be funded elsewhere due to the rarity of the disease.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 15	• The proposed project has sound scientific and clinical rationale. • The preliminary data is strong and justifies continued development of product. The authors have shown reasonable on-target and off-target effects. The preclinical data has shown correction of patient-derived T cells. Whether they can correct CD34+ HSCs remains to be seen but will be proven through this very well-written proposal. • The tight regulation of gene expression is a strength.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 15	• The plan appropriately incorporates feedback from the applicant FDA INTERACT meeting, with well-constructed milestones and endpoints based on the preliminary data presented. • This proposal is a logical extension of this groups' previous work. This method might be important in a number of similar diseases. • While a clinical protocol may be helpful, the applicant should consider proceeding with a detailed clinical synopsis at this stage. The proposed development of a clinical protocol, investigator's brochure, and consent forms should be gated to a successful completion of IND-enabling studies and feedback received from a pre-IND meeting. • A potentially excessive amount of money seems to have been allocated for project management.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 15	• The studies are well organized and sequenced to complete the work in the three year time frame. • The project has a clear path forward with a high chance of success based on a very helpful and informative FDA INTERACT meeting. • The team is appropriately qualified and staffed, and the team members are very highly qualified with excellent track records. • Off-target analysis is always an issue with gene editing, but this team has a good chance of solving these issues. • Given the ultra orphan nature of the disease, future clinical trial enrollment would be important to account for in development planning.
No: 0	*none*

Application #	TRAN1-11555
Title (as written by the applicant)	BCMA/CS1 Bispecific CAR-T Cell Therapy to Prevent Antigen Escape in Multiple Myeloma
Translational Candidate (as written by the applicant)	A single-chain bispecific chimeric antigen receptor (CAR) targeting BCMA and CS1 will be used to in autologous T-cell therapy for multiple myeloma.
Area of Impact (as written by the applicant)	Translational candidate will enable treatment of patients with heterogeneous or BCMA– multiple myeloma and prevent cancer relapse due to antigen loss.
Mechanism of Action (as written by the applicant)	BCMA and CS1 are markers commonly found on multiple myeloma (MM) cells. Here, patient-derived naïve/memory T cells enriched in stem-cell memory phenotype are engineered to express a BCMA/CS1 bispecific chimeric antigen receptor (CAR), which triggers robust T-cell activation and anti-tumor effector function upon recognizing either BCMA or CS1 on the surface of target cells. The bispecific CAR-T cell can efficiently eliminate MM tumor cells even if they had lost expression of either BCMA or CS1.
Unmet Medical Need (as written by the applicant)	Multiple myeloma (MM) is an incurable disease. CAR-T cell therapy targeting BCMA shows clinical promise against MM, but many patients have BCMA-negative tumors or develop BCMA-negative MM after treatment. BCMA/CS1 bispecific CAR-T cells can prevent tumor escape to increase clinical efficacy.
Project Objective (as written by the applicant)	Pre-IND meeting; readiness for GMP manufacturing.
Major Proposed Activities (as written by the applicant)	• Rodent studies to determine optimal T-cell dosing regimen and compare BCMA/CS1 bispecific CAR with bb2121 (a clinically tested single-input BCMA CAR) • Cell-culture and rodent studies to identify any propensity for the Therapeutic Candidate to cause cytokine release syndrome and off-tumor toxicity • Demonstration of GMP-compatible cell manufacturing and completion of clinical protocol and internal regulatory filings
Statement of Benefit to California (as written by the applicant)	Multiple myeloma afflicts >32,000 new patients in the US and leads to >1,200 deaths in California each year. A therapy with robust and durable efficacy against this otherwise incurable disease will not only improve the well-being of Californians, but also reduce the substantial medical costs associated with long-term and ultimately ineffective treatments. This will reduce burden on the state's medical system and enable redirection of resources to other areas of unmet needs.
Funds Requested	$3,176,805
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

SCORING DATA

Final Score: 85

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

Mean	83
Median	85
Standard Deviation	5
Highest	88
Lowest	65
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	10
(1-84): Not recommended for funding	5

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific members of the GWG were asked to

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

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• While the CAR-T field has made lots of advances, there remain many challenges, and this program can answer many important questions for the field and provide a big impact for patients. • The project is designed to generate second generation CAR-T cells targeting two antigens. Multiple myeloma treatment currently includes several novel targeted agents. It is likely that bb2121 (anti-BCMA CAR-T) will be approved soon, however, early data suggest that this approach is not durable in most patients. The major unmet need in the disease is the availability of therapies capable of producing prolonged remissions, especially in advanced patients. There is also a need for broadly applicable curative therapies. It is possible that the proposed approach can meet the first unmet need, but unlikely to address the second.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 10	• The bispecific CAR approach would expand the number of patients that could benefit from this treatment and may reduce costs as 2 patients subsets could be treated with a single product. • Both the BCMA and CS1 targets are supported in the literature (and clinical trials) and the rest of preclinical data is good. • The approach to dual targeting with one CAR-T is attractive. While multiple groups have attempted this concept, this application presents an approach that is most likely to achieve success. • There are some doubts about whether CS1 is a target that will likely improve efficacy.
No: 4	• Antigen loss of CS1 may also occur. • It is unclear whether CS1 is a useful target along with BCMA.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 12	• The program is well designed, and based on the previous experience developing a CD19/CD20 CAR. The program is well positioned for success. • The timeline is feasible and the studies are rational and well designed to achieve meaningful outcomes and lead to a potentially successful pre-IND meeting. • The available data does not support enrichment for T memory/stem cells as beneficial for CAR-T efficacy (bulk T-cells will contain requisite subsets). • The data regarding the fratricide experiments is confusing based on the proposed mechanism for how this product works. The results are unexpected and thus more investigation may be needed.
No: 2	• The rationale for the BCMA CAR-T cell and anti-PD1 antibody combination treatment in the proposed preclinical testing is unclear. • The CRS modeling study is not necessary. • CD62L fractionation is not necessary and adds complexity.
GWG Votes	**Is the proposal feasible?**
Yes: 14	• The team has excellent experience in this area. • Manufacturing and other contracts appear to be in place and ready to go. Timelines are appropriate. • The program is considered low-risk in terms of achieving a successful pre-IND meeting. • Additional expertise in the biology of myeloma would be helpful.
No: 0	*none*

Application #	TRAN1-11544
Title (as written by the applicant)	Neural stem cell-mediated oncolytic immunotherapy for ovarian cancer
Translational Candidate (as written by the applicant)	A clinically tested tumor-tropic neural stem cell (NSC) platform for effective distribution of oncolytic virotherapy to ovarian cancer metastases
Area of Impact (as written by the applicant)	This NSC-delivered virotherapy approach will lead to a more efficacious, less toxic treatment for metastatic ovarian cancer and chemoresistant cells.
Mechanism of Action (as written by the applicant)	CRAd-S-pk7 is a tumor specific replication-competent adenovirus driven by a survivin promoter, which is constitutively highly expressed in ovarian cancer cells. We will use our tumor-tropic/tumor-penetrating NSC platform to produce the oncolytic virus within ovarian metastases. Viral replication will lyse cancer cells and infect neighboring cancer cells, thus amplifying its effect until reaching normal tissue. We will also stimulate a secondary immune response to newly exposed tumor antigens.
Unmet Medical Need (as written by the applicant)	Most ovarian cancer patients present late stage with abdominal metastases, and can't complete chemotherapy due to severe toxicity and chemoresistance. NSCs will more effectively target and distribute an oncolytic virus, selectively lysing cancer cells and stimulating an anti-tumor immune response.
Project Objective (as written by the applicant)	Pre-IND meeting; ready for GMP clinical lot.
Major Proposed Activities (as written by the applicant)	• In vivo determination of dosing regimen (multiple rounds) for maximal therapeutic efficacy • In vivo determination of secondary immune response, following oncolysis of tumor cells • In vivo determination of preliminary safety/toxicity profile
Statement of Benefit to California (as written by the applicant)	Ovarian cancer is the most lethal gynecologic malignancy, resulting in 1,500 deaths annually in California. At diagnosis, >70% of patients already have metastases throughout their abdomen, leading to a dismal 34% 5-year survival rate. We anticipate that our stem cell-delivered oncolytic virotherapy will lead to a more effective, less toxic treatment for these patients that will kill even metastatic tumor foci and chemoresistant cells, improving survival of ovarian cancer patients in California.
Funds Requested	$2,873,262
GWG Recommendation	***(85-100): Exceptional merit and warrants funding, if funds are available***

SCORING DATA

Final Score: 85

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

Mean	83
Median	85
Standard Deviation	6
Highest	90
Lowest	70
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	9
(1-84): Not recommended for funding	6

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in

the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 14	• There is a tremendous unmet medical need for new treatments for recurrent and late stage metastatic ovarian cancer. • If the therapy is successful, it would be important advance that could be used after other methods have been tried. • There is a lot of excitement for this novel approach.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• This project is based on multiple years of studying the ability of NSCs to be used as anti-tumor reagents, and the surprising finding that they also can be applied to the treatment of tumors outside of the central nervous system. • While oncolytic viruses can efficiently infect and kill cancer cells, their delivery is a challenge as most of the population has pre-existing antibody against the vectors. The stem cells in this case are key to the treatment. The data presented in this proposal suggest that the NSC cells are naturally homing to the cancer cells, delivering the virus and allowing the vector to retain its therapeutic efficacy by escaping neutralizing antibodies. • Using a cellular vector to try and protect adenovirus from immune neutralization is an interesting idea, and targeting adenovirus expression to cells with an active survivin promoter would offer a measure of specificity. The applicant says that survivin is expressed in 85% of chemo resistant ovarian cancer patients, but does not discuss whether expression is seen in all cancer cells and particularly whether expression is seen in cancer stem cells. This information would be helpful in understanding the utility of this approach. • The new generation antivirus constructs being employed in this study have been designed to overcome limitations of previous viruses. • The significant reduction in tumor weight demonstrated in Fig 6d is a strength. • The weakness is that they have not demonstrated increased survival of tumor bearing mice. • Will the NSCs be rejected by the patient's innate immune system? It appears this risk is minimized and further examined in this proposal. These studies will be critical in the pre-clinical studies to be sure that NSCs will not be rejected by the innate immune system.
No: 2	• It is unclear if these modified cells will be rejected in humans. There is potential rejection from NK cells given the cells don't express HLAs, which is not discussed in the proposal.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 13	• The project is well designed and based on extensive prior knowledge. The pre-clinical experiments proposed by the team will lead to the selection of the initial dose to be used in the clinical trial. • The studies are well-designed and have a high chance of success. The major hurdle relates to the potential for immune rejection by the NK cell and innate immune compartment. • A meeting with FDA would be helpful to better understand the demonstration of preclinical efficacy that would be required for the FDA to allow an IND and ensure that the planned studies provide that. • It is well planned, but high risk and high reward.
No: 2	• There is an absence of any efficacy data in the proposal which is a critical flaw.
GWG Votes	**Is the proposal feasible?**
Yes: 14	• Continued development appears justified despite the acknowledged challenges of generating supportive pharmacology data in animals. • The path to pre-IND appears reasonable and consistent with FDA expectations. • The PI has previous preclinical and clinical expertise with this platform in another indication. • This is an excellent team that has significantly advanced the field. • All of the pieces are in place to move this project forward efficiently.
No: 1	• Extended survival has not been demonstrated in any animal model. • It is unclear whether the cells will be invisible to the immune system.

Application #	TRAN1-11611
Title (as written by the applicant)	Development of a human stem cell-derived inhibitory neuron therapeutic for the treatment of chronic focal epilepsy
Translational Candidate (as written by the applicant)	A cellular therapeutic comprised of inhibitory nerve cells produced from human stem cells
Area of Impact (as written by the applicant)	Drug-resistant chronic temporal lobe epilepsy
Mechanism of Action (as written by the applicant)	The product candidate is intended to be delivered into the seizure focus, integrate, and secrete the inhibitory neurotransmitter GABA to rebalance neural electrical activity in the brain and eliminate/reduce seizures.
Unmet Medical Need (as written by the applicant)	The seizures in approximately one-third of epilepsy patients do not adequately respond to current anti-epileptic drugs. Alternative surgical interventions are highly invasive and damage brain tissues. The proposed product candidate is intended to be restorative and long-acting.
Project Objective (as written by the applicant)	Pre-IND meeting; Pilot material manufactured
Major Proposed Activities (as written by the applicant)	• Finalize manufacturing process to be appropriate for future clinical use • Produce Pilot product using the intended process, confirm efficacy in two rodent models of chronic epilepsy and demonstrate safety at maximum dose • Select intended clinical cell delivery device and conduct pre-IND meeting to confirm IND-enabling preclinical requirements
Statement of Benefit to California (as written by the applicant)	Epilepsy is the fourth most common neurological disorder affecting more than 400,000 people in the State of California. One-third of epilepsy patients are considered to be drug-resistant and have persistent, uncontrolled seizures that can be disabling and affect quality of life. Alternative surgical interventions are highly invasive and may cause lasting impairment. This proposal aims to further develop a cellular therapeutic for treating drug-resistant epilepsy.
Funds Requested	$5,246,287
GWG Recommendation	***(1-84): Not recommended for funding***

SCORING DATA

Final Score: 78

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

Mean	76
Median	78
Standard Deviation	6
Highest	84
Lowest	60
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

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

Yes: 14	• Temporal lobe epilepsy is an important need, and it is good to see someone working on a solution in this area. However, there is lack of clarity around the patient benefit and the true clinical goal. • The concept of inhibitory interneurons in this space is a good one, and has potential applications in other areas such as chronic pain. While it may be a difficult path to translation for this product, this project may assist in developing stem cell technologies outside of refractory epilepsy. • The treatment is likely to be economically valuable.
No: 1	*none*
GWG Votes	**Is the rationale sound?**
Yes: 10	• The plan and proposal to use inhibitory neurons makes sense. • Many of the current surgical procedures have only a 50-60% long-term efficacy. Current advanced imaging shows that these seizures are more complex than one small area. It is unclear how the proposed treatment at a single site would be better than the current procedure. • A possible MRI compatible device for delivery is proposed. However, conventional stereotaxis is extremely accurate and seems unnecessary. The volume and rate of delivery are more important considerations for possible tissue damage.
No: 5	• The target reduction of seizures they are aiming for seems small, and may be easier to achieve in the animal models than in humans.
GWG Votes	**Is the proposal well planned and designed?**
Yes: 3	*none*
No: 12	• The proposed animal models don't use medications as controls as they would be used in the clinic. It is unclear if this is because the animal models don't have a response to medications or not. Even if they do not, this may be a missed opportunity to see an effect, ie. changing treatment-resistant to treatment-sensitive. • The cell derivation and sorting process with proprietary antibodies is complex and adds risk to the project. • Manufacturing aspects were difficult to assess as very few manufacturing details were provided. We tried very hard to get details on the CMC section but the applicants were not forthcoming.
GWG Votes	**Is the proposal feasible?**
Yes: 9	• There were challenges in evaluating the feasibility of CMC/manufacturing based on the information provided. • The team seems good, engaging several CROs.
No: 6	• The applicant will be dependent on CROs to meet the timelines. • Feasibility was unclear because of the lack of details in the application.