

TRANSLATIONAL AWARDS

\$13,415,719 GWG RECOMMENDED

APP #	TITLE	BUDGET REQ	FUND?	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Resubmission	Previous CIRM Funding	Disease Indication	Product Type	Approach
TRAN1-10416	DEBCT: Genetically Corrected, Induced Pluripotent Cell-Derived Epithelial Sheets for Definitive Treatment of Dystrophic Epidermolysis Bullosa	\$5,560,615	Y	90	90	3	84	95	14	1	N	Y	Epidermolysis Bullosa	Gene-modified cell therapy	Autologous, collagen gene-corrected, iPSCs-derived keratinocytes
TRAN1-10587	Human Embryonic Stem Cell-Derived Natural Killer Cells for Cancer Treatment	\$5,154,684	Y	90	90	3	85	93	12	0	Y	N	Acute myeloid leukemia	Cell therapy	hESC-derived (allogeneic) NK cells targeting cancer cells
TRAN1-10540	A Splicing Modulator Targeting Cancer Stem Cells in Acute Myeloid Leukemia	\$2,700,420	Y	90	88	3	84	90	13	1	Y	Y	Acute myeloid leukemia	Small molecule	RNA splice-modulator inhibitor acting on CSC survival genes
TRAN1-10422	cGMP-grade placental stem cell production and characterization for treatment of congenital metabolic disorders	\$5,943,061	N	80	80	6	65	90	4	11	N	Y			
TRAN1-10427	Human Amniotic Fluid Stem Cell derived Extracellular Vesicle (hAFSC-EVs) for the treatment of Alport Syndrome	\$4,886,544	N	75	73	5	60	80	0	14	N	Y			
TRAN1-10434	Development of an Effective Mobilizer of Stem Cells	\$2,945,300	N	72	71	5	60	75	0	14	Y	Y			
TRAN2-10449	Development of a Noninvasive Prenatal Test for Beta-Hemoglobinopathies for Earlier Stem Cell Therapeutic Interventions	\$1,721,808	N	70	68	11	30	75	0	15	N	N			
TRAN1-10413	Retinal Progenitor Cells for Treatment of Diabetic Retinopathy	\$4,741,411	N	-	-	-	-	-	0	15	N	Y			
TRAN1-10567	Therapeutic development of Oxy200, an oxysterol with bone anabolic and anti-resorptive properties for intervention in osteoporosis	\$1,757,830	N	-	-	-	-	-	0	14	N	N			
TRAN1-10624	Pre-clinical development of a small molecule for the treatment of osteoarthritis	\$2,837,604	N	-	-	-	-	-	0	15	Y	Y			



Application #	TRAN1-10416
Title (as written by the applicant)	DEBCT: Genetically Corrected, Induced Pluripotent Cell-Derived Epithelial Sheets for Definitive Treatment of Dystrophic Epidermolysis Bullosa
Translational Candidate (as written by the applicant)	DEBCT is an autologous iPS-derived COL7A1-corrected keratinocyte graft indicated for the treatment of all chronic open wounds in patients with RDEB.
Area of Impact (as written by the applicant)	RDEB patients lack type VII collagen and have chronic wounds that lack an abundance of keratinocyte stem cells. DEBCT skin grafts will close wounds.
Mechanism of Action (as written by the applicant)	RDEB patient keratinocytes contain mutations in COL7A1, lack the adhesion protein type VII collagen, and suffer profound skin fragility, chronic open wounds, and stem cell depletion. DEBCT is a COL7A1-corrected autologous keratinocyte stem cell sheet, when grafted onto wounds, adhere tightly and provide long-term wound closure. Autologous, corrected iPS cells can be grown in large quantities and can be induced to produce keratinocyte stem cells, allowing clinical scaling and manufacturing.
Unmet Medical Need (as written by the applicant)	Children with the debilitating inherited blistering disorder Recessive Dystrophic Epidermolysis Bullosa lack the COL7A1 gene and experience painful non-healing wounds over their body, and risk death from cancer later in life. Current therapy is palliation costing thousands of dollars per month.
Project Objective (as written by the applicant)	Pre-IND meeting and DEBCT pivotal study plan
Major Proposed Activities (as written by the applicant)	<ul style="list-style-type: none"> • Optimize cGMP-compatible one step reprogramming and correction to autologous IPS cells and develop cGMP-compatible nucleic acid reagents • Optimize coupling efficiency of COL7A1-corrected iPS-derived graftable keratinocytes and develop cGMP-compatible CD49f cell separation protocol • Perform rodent pilot efficacy and safety studies of DEBCT keratinocyte grafts prior to a Pre-IND FDA meeting
Statement of Benefit to California (as written by the applicant)	While Epidermolysis Bullosa is a rare orphan disease, many of the common alleles are found in people of Latin American descent, a significant population in California. Children with the debilitating inherited blistering disorder experience painful non-healing wounds over their body, with current palliative therapy costing thousands of dollars per month. Long-term wound closure with DEBCT, a therapy developed in California, would lead to lower overall health costs and improved quality of life.
Funds Requested	\$5,560,615
GWG Recommendation	<i>(85-100): Exceptional merit and warrants funding, if funds are available</i>

Scoring Data

Final Score: 90

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	90
Median	90
Standard Deviation	3
Highest	95
Lowest	84
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	14
(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 the necessary significance and potential for impact?	12	0	1
Is the rationale sound?	12	0	1
Is the proposal well planned and designed?	10	0	3
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

- Strong unmet medical need
- Strong case around the unmet medical need
- Good target disease
- RDEB is a severe disease that lends itself to utilizing cutting edge therapeutics like iPSCs - the risk is worth the potential benefit to the patient population
- This program addresses a serious unmet need with strong rationale and supporting data

- Novel approach addressing key limitations in the field (elimination of murine feeders, xeno products, integrating vectors)
- State of the art and clinically applicable system, excellent clinical data
- Strong clinical evidence
- Built upon prior clinical trial data
- New methods proposed improve efficacy
- The improvements in the manufacturing process are definitely a step in the right direction. The group has made good progress in this area.

- Potential to impact field of iPSC-derived therapeutics beyond target disease in this study
- Overall a good plan, based on an excellent premise
- Good experimental plan

- Outstanding team of investigators
- Outstanding investigator group

Concerns

- There is a risk of karyotypic aberrations (p53 mutations in literature) with culture (although investigators suggest StemKit will address problem)
- There is a risk of chromosomal abnormalities when making iPSCs
- Potential for chromosomal abnormalities with iPSC-based technology

- Xenografts onto NSG immunocompromised mice are a validated preclinical model for human epithelial sheet formation. Reviewers would have liked to see the preclinical data.
- Wound healing in mice is fast, perhaps a better transgenic model would guide efficacy endpoints.
- FDA correspondence asked for an 'n' of 10 or larger and the FDA wanted life time of the animal safety studies, neither is proposed here.

- Addresses only the cutaneous manifestations of the disease (not esophageal, mucosal disease)
- The timelines may be a bit overambitious
- Complex project to complete within timeline



Application #	TRAN1-10587
Title (as written by the applicant)	Human Embryonic Stem Cell-Derived Natural Killer Cells for Cancer Treatment
Translational Candidate (as written by the applicant)	Human embryonic stem cell (hESC)-derived natural killer (NK) cells to target relapsed/refractory Acute Myelogenous Leukemia (AML)
Area of Impact (as written by the applicant)	hESC-derived NK cells provide a novel and potent approach to treat relapsed or refractory AML that is resistant to current chemotherapy options.
Mechanism of Action (as written by the applicant)	hESC-derived NK cells provide a standardized, homogeneous, off-the-shelf cellular immunotherapy product that will be used as an allogeneic adoptive transfer treatment for patients with AML who have either never achieved remission with standard induction therapy, or who relapse after previous chemotherapy. hESC-derived NK cells kill tumor cells by several mechanisms: direct cytotoxicity, antibody-dependent cell-mediated cytotoxicity, induction of apoptosis and production of cytokines.
Unmet Medical Need (as written by the applicant)	Over 10,000 in the US die each year from AML, with 5 year survival <30%. Allogeneic NK cells are known to destroy AML cells in patients who have failed chemotherapy. hESC-derived NK cells will provide the first standardized, "off-the-shelf" cellular immunotherapy to treat this deadly disease.
Project Objective (as written by the applicant)	The objective is to have an FDA Pre-IND meeting
Major Proposed Activities (as written by the applicant)	<ul style="list-style-type: none"> We will use the GMP hESC line ESI-017 to produce a Master Cell Bank and Working Cell Bank of NK cells using defined clinical-scale cell methods. We will demonstrate ESI-017 hESC-derived NK cells kill AML tumor cells 1) in vitro, and 2) in vivo using NSG mouse xenograft models. We will assess safety of ESI-017 hESC-derived NK cells using NSG mouse model and in vitro assays to test tumorigenicity and lack of off-target killing
Statement of Benefit to California (as written by the applicant)	Over a thousand Californians are diagnosed with Acute Myeloid Leukemia (AML) each year, and five year survival in California is less than 30%. New treatment options are desperately needed for patients who fail standard chemotherapy. We will produce a standardized, off-the-shelf immunotherapy cell product that can induce remissions and lead to cure of AML. These studies with hESC-derived NK cells will allow Californians to be at the forefront of this cellular immunotherapy approach to treat AML
Funds Requested	\$5,154,684
GWG Recommendation	(85-100): Exceptional merit and warrants funding, if funds are available

Scoring Data

Final Score: 90

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

Mean	90
Median	90
Standard Deviation	3
Highest	93
Lowest	85
Count	12
(85-100): Exceptional merit and warrants funding, if funds are available	12
(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 the necessary significance and potential for impact?	9	0	0
Is the rationale sound?	9	0	0
Is the proposal well planned and designed?	9	0	0
Is the proposal feasible?	8	0	1

Reviewer Comments

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

Strengths

- Overall, NK cells should have an excellent safety profile based on previous human studies; an off-the-shelf option would be a major step forward for the field
- The product characteristics and benefits are well defined in vitro and in vivo
- Good target disease
- Homogeneous cell product
- Good preliminary data

- Addressed all previous concerns of reviewers and FDA recommendations
- Very responsive to previous application
- Excellent job addressing previous reviewer comments
- The applicant has done an excellent job incorporating reviewer comments as well as FDA expectations outlined in the pre-pre-IND meeting minutes
- Very strong team, multidisciplinary and can take the product to therapy

Concerns

- Off target effects. i.e., specificity for leukemic blasts should be documented in vivo
- Consider adding in-testing of NK toxicity with normal CD34+ cell xenografts (NSG models)
- Not yet demonstrated in vivo assessment of the product's safety versus normal hematopoietic cells
- A lot of NK products already available



Application #	TRAN1-10540
Title (as written by the applicant)	A Splicing Modulator Targeting Cancer Stem Cells in Acute Myeloid Leukemia
Translational Candidate (as written by the applicant)	17S-FD-895 is a potent small molecule splicing modulator that inhibits aberrant splicing in CSCs that have deregulated SF3B1 expression.
Area of Impact (as written by the applicant)	Development of 17S-FD-895 could address a major bottleneck to reducing AML mortality by targeting splicing deregulated-CSCs that fuel AML relapse.
Mechanism of Action (as written by the applicant)	17S-FD-895 will positively impact patients with AML by providing a potent and selective CSC-targeted therapeutic strategy that could prevent relapse and improve overall survival. In addition, splice isoform biomarkers of CSC response to 17S-FD-895 have already been identified. Through targeted modulation of the RNA splicing machinery, we can alter and monitor the splicing response to 17S-FD-895, which provides a vital companion diagnostic for proof-of-concept studies in future clinical trials.
Unmet Medical Need (as written by the applicant)	Despite recent advances in molecular targeted and immunotherapeutic strategies, patients with AML have a 5 year life expectancy of only 26% due to high relapse rates fueled by CSCs. CSCs are uniquely sensitive to splicing modulation and can be selectively inhibited by 17S-FD-895.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	<ul style="list-style-type: none"> • Manufacture sufficient quantities of 17S-FD-895 to complete key pre-IND studies • Complete non-clinical safety and toxicology studies, pre-clinical studies and biomarker testing as proof-of-concept for future clinical applications • Complete pre-IND studies and have a pre-IND meeting
Statement of Benefit to California (as written by the applicant)	For nearly 50 years, no therapies have significantly reduced relapse-related mortality in acute myeloid leukemia (AML). The rapid lethality of AML relapse is underscored by the fact that in California in 2014 there were 1,112 deaths from AML and 1,614 new patients diagnosed. A selective cancer stem cell-targeted agent, 17S-FD-895, offers a novel therapeutic candidate for AML patients and those suffering from other recalcitrant cancers, providing hope for many of our fellow Californians.
Funds Requested	\$2,700,420
GWG Recommendation	<i>(85-100): Exceptional merit and warrants funding, if funds are available</i>

Scoring Data

Final Score: 90

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	88
Median	90
Standard Deviation	3
Highest	90
Lowest	84
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	13
(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 the necessary significance and potential for impact?	8	0	2
Is the rationale sound?	8	0	2
Is the proposal well planned and designed?	8	0	2
Is the proposal feasible?	5	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

- Clearly an unmet medical need. Still poor survival in this leukemia population
- This is a novel approach to AML treatment and has exciting potential
- Strong underlying science
- Very comprehensive response to prior review comments
- This is a strong proposal that took many of our previous comments into account
- Have responded well to previous round of reviews
- Safety issues to some extent addressed in revision
- Drug is well characterized
- Mechanism of action is well defined
- Splice isoforms profile as biomarkers of response: excellent!
- Use of humanized mouse models is important
- Contingency plan is excellent
- Very impressive group with excellent track record of previous successes in previous CIRM funding

Concerns

- The major potential risk in the tolerability studies is visual toxicity as noted by the PI, and the animal models to test the drug need to be validated; using previous splicing modulators which caused visual issues would work as a positive control
- There is still concern that the safety species proposed may not translate to humans with regard to ocular toxicity observed with E7107; it is critical that the submitter demonstrate ocular toxicity with E7107 in the rat, large animal, and/or rabbit
- Should test in combination with chemotherapy agents
- Little functional data
- The 'n' appears to be very small in several of the studies
- Milestones are defined but very numerous; there is concern they may not be completed in time
- The timelines may be a bit over ambitious



Application #	TRAN1-10422
Title (as written by the applicant)	cGMP-grade placental stem cell production and characterization for treatment of congenital metabolic disorders
Translational Candidate (as written by the applicant)	We will produce therapeutic grade placental stem cells that possess hepatic differentiation capability and contain abundant lysosomes.
Area of Impact (as written by the applicant)	Cell replacement therapy for congenital metabolic disorders will be possible with the non-tumorigenic and readily available placental stem cells.
Mechanism of Action (as written by the applicant)	Upon liver-directed cell transplantation, the engrafted placental stem cells (hAECs) will differentiate to hepatic cells and provide hepatic and lysosomal metabolic enzyme functions. By compensating for the patient's missing enzyme function, the disease symptoms will be improved.
Unmet Medical Need (as written by the applicant)	Currently, there are no definitive therapies for congenital metabolic disorders. These disorders can be treated by hAEC transplantation.
Project Objective (as written by the applicant)	Obtain data for successful pre-IND meeting
Major Proposed Activities (as written by the applicant)	<ul style="list-style-type: none"> Isolate hAECs with a clinically applicable protocol under cGMP conditions Evaluate the quality and therapeutic potential of isolated cells Catalog the therapeutic grade hAECs with the HLA type and cryopreserve them to produce a Bio-Bank
Statement of Benefit to California (as written by the applicant)	If successful, the proposed project will lead to initiating a novel stem cell therapy for congenital metabolic disorders in California. Therefore, the potential benefits will be 1) providing the new therapy to the Californian patients with unmet medical needs, 2) increasing visiting patients from outside of the State for the treatment, and 3) creation of new cell therapy related medical industry jobs for Californians.
Funds Requested	\$5,943,061
GWG Recommendation	<i>(1-84): Not recommended for funding</i>

Scoring Data

Final Score: 80

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

Mean	80
Median	80
Standard Deviation	6
Highest	90
Lowest	65
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	4
(1-84): Not recommended for funding	11

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have the necessary significance and potential for impact?	12	0	1
Is the rationale sound?	6	3	4
Is the proposal well planned and designed?	1	7	5
Is the proposal feasible?	3	5	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

- A clear unmet medical need
- Novel approach

- This is a possible new category of stem cells that could provide major clinical impact
- The cells appear to be useful for multiple clinical indications
- The applicant selected very appropriate diseases for study
- Interesting cell type and targets
- Interesting and potentially powerful stem cell option
- Interesting cell type for transplantation - avoids issues related with pluripotent stem cell-derived cell therapies
- Very interesting cell type which overcomes several negative aspects of embryonic stem cells
- Opportunity for multiple clinical indications; opportunity to leverage data across multiple indications
- Better than enzyme replacement or transplantation of hepatocytes

- Immunologic advantages in using these cells
- Down-regulation of human leukocyte antigen (HLA) mediated effects
- Favorable immune effects
- Limited tumorigenicity is observed
- Only modest cell engraftment is needed for beneficial effects
- Cells are easily available

- Manufacturing process is adequate
- Good animal data to support efficacy
- Trial in Europe (already have IRB approval for 10 patients) could provide insights that influence pre-IND meeting
- The clinical trial that is being run in Europe should give a strong basis for the clinical trials.

Concerns

- Some animal testing needs to be done in an immune competent model
- Work in additional species would be helpful
- All studies are in rodent models; often in immunodeficient or syngeneic animals
- Would like to see more details of the animal studies; testing in older animals closer to what may occur in humans would be helpful
- Treatment in immature mice with immature livers may not translate well to people; other models should be tested with more mature livers, similar to patients
- It is not clear if cells will engraft the in the same numbers in older animals
- Animal study data was weak, another animal model should be used in proof of concept testing to demonstrate cell function in older animals
- Very little "own" preliminary data (most of the animal data generated by applicant is not published)

- Applicant needs to define clearly the expectation for engraftment and required frequency of treatments to maintain an effective dose
- There is little discussion of risks, including the longevity of the engrafted cells

- The durability of the treatment appears unknown
- There are concerns related to the durability of treatment in humans
- Concerns about the loss of immune modulation after engraftment/differentiation were not addressed in application
- Additional data is needed to support lack of immune response of final differentiated cell product
- It is unclear if the immunologic advantages are still present when the cells mature in vivo
- A more rigorous risk assessment is needed
- Perhaps too ambitious a project: focus on one metabolic disease may be helpful
- Focusing on the metabolic disorders that don't have currently available therapies is recommended; the probability of success is relatively higher with the greatest unmet medical need and should also assist w/ reasonable timeline

- Regulatory strategy should be reviewed; targeting multiple diseases is not a good idea and the team should focus on a single indication and review strategy for the U.S.
- The application would benefit from a stronger regulatory strategy; for example, it is not clear what the target indication is for the pre-IND meeting
- A clear understanding of the regulatory requirements for manufacturing scale-up was not demonstrated
- Need stronger input from someone with experience with regulatory bodies
- Regulatory input was weaker than expected
- Applicant would benefit from a pre-pre-IND in order to obtain additional regulatory advice
- Applicant should consider additional studies to support a pre-IND meeting
- Donor eligibility criteria did not appear to be met for US FDA regulations (21CFR 1271)

- Human leukocyte antigen (HLA) matching strategy was not well thought out - are making 50 cell lines and then doing HLA typing
- It was not clear if the 50 HLA typed hAECs would have a meaningful clinical impact
- HLA coverage of the cells banks should be addressed
- HLA matching issue: should do before banking
- The ability to manufacture large quantities of cells is unproven
- Unproven track record in mass production of cells
- Transferring the process to the U.S. and manufacturing all of the proposed cell banks is a big concern
- Quality control testing not adequately addressed

- Timeline is likely not reasonable for establishing 50 master cell banks as cell bank testing is going to be pretty significant - but should discuss with the FDA
- Too many cell lines planned; may not be feasible
- Tight and unrealistic timeline
- Very aggressive timeline for this approach
- Several practical issues reduce feasibility



Application #	TRAN1-10427
Title (as written by the applicant)	Human Amniotic Fluid Stem Cell derived Extracellular Vesicle (hAFSC-EVs) for the treatment of Alport Syndrome
Translational Candidate (as written by the applicant)	Human Amniotic Fluid Stem Cell derived Extracellular Vesicles (hAFSC-EVs) with renal-protective activity.
Area of Impact (as written by the applicant)	hAFSC-EVs would treat glomerular sclerosis in patients affected by chronic kidney disease, like Alport Syndrome for which there is no cure.
Mechanism of Action (as written by the applicant)	Our goal is to develop an effective therapy to treat patients that suffer from Alport Syndrome, a chronic kidney disease. We propose to use human amniotic fluid stem cell derived extracellular vesicles (hAFSC-EVs) as new product for the treatment of glomerular sclerosis. hAFSC-EVs can be considered "off the shell" product that, once injected, can restore normal glomerular function by localized downregulation of Vascular endothelial growth factor (VEGF), thus delay/reverse progression of chronic kidney disease.
Unmet Medical Need (as written by the applicant)	There is no effective treatment to slow or halt the progression of chronic kidney disease. hAFSC-EVs will slow or halt the progression to end stage renal disease in Alport Syndrome patients. This will improve the patient's quality of life and delay kidney transplants.
Project Objective (as written by the applicant)	Effective Pre-IND meeting with FDA.
Major Proposed Activities (as written by the applicant)	<ul style="list-style-type: none"> • Manufacturing process development and generation of MCB of hAFSC-EVs to support Phase I and Phase II trial • Performing efficacy, toxicity and safety studies in pre-clinical animal models of Alport Syndrome. • Collection and evaluation of all data for the Pre-IND meeting with the FDA
Statement of Benefit to California (as written by the applicant)	The State of California spends yearly million of dollars in dialysis treatments and in kidney transplants. Our child and adult patients will greatly benefit from a tolerable, safe but most importantly effective therapy preventing renal failure. California will benefit from the highly reduction in medical costs, and this discovery will place the State as one of the major centers in the Nation for the treatment of this devastating disease, which ultimately will contribute to economical growth.
Funds Requested	\$4,886,544
GWG Recommendation	(1-84): Not recommended for funding

Scoring Data

Final Score: 75

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

Mean	73
Median	75
Standard Deviation	5
Highest	80
Lowest	60
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion

influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have the necessary significance and potential for impact?	9	0	4
Is the rationale sound?	5	6	2
Is the proposal well planned and designed?	1	3	9
Is the proposal feasible?	1	4	8

Reviewer Comments

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

Strengths

- Strong unmet medical need for disease
- Clear unmet need
- Medical need is well defined
- Good target disease

- Novel approach
- This is a new and exciting approach
- Interesting concept - potential for an innovative therapy
- Data presented is exciting

- Relevant pre-clinical model
- Animal models are fairly convincing
- The animal model that was selected for the studies is a validated model of Alport Syndrome
- The large animal model offers a clear advantage of providing additional information beyond just using rodents
- Preclinical testing will treat animals at different stages of the disease which is important
- They plan to compare this product to the current standard of care treatment in large animal models which may help to suggest a mechanism of action
- A good potency assay has been developed
- Mechanism of action for EVs is good
- Appears to be safe

- Lab environment is good
- The team has the expertise needed to advance the project successfully once the issues are addressed

Concerns

- Since patients will be treated with the standard of care + EV, a group of mice to test both should be added; this may help to inform the large animal studies as well
- Teratoma testing should also be done in immune-compromised mice
- It is unclear why, if venous delivery doesn't work well, femoral artery delivery in the large animal model below the level of the kidneys is used; a catheter to the aortic arch or least above the kidneys would be easy and safe to do for delivery and would increase 'n' for the other experiments
- A better understanding of the point of administration and impact on in vivo EV biodistribution is needed; the current route of administration will likely end up with the majority of the EVs lodged in the pulmonary bed and therefore not likely providing a benefit to the animal/patient

- EVs in vivo targeting needs to be established
- In the large animal studies, using the ultrasmall superparamagnetic iron oxide particles to track the EV's will be challenging and it is unclear whether labeling has been tested
- It is unclear whether MRI will be sensitive enough to see the small amounts of EV in tissue and whether artifacts can be differentiated from the real signal; some preliminary data here would be good

- Use of IVIS to track the EV will be challenging, due to the amount of EV remaining after a few hours/days and the depth of the EVs in the animal; would like to see preliminary images showing this is possible
- In the large animal studies, the dosing in the safety and toxicity analysis is not clear; this could be done in a good laboratory practice (GLP) lab or check with the FDA prior to starting these studies to determine if these will be acceptable for at least the pre-IND or preferable for the IND filing
- The "Assessment of dose" milestone is not well described in the project plan; better planning for the dose-finding and mechanism studies is required

- Need additional animal studies for validation of the concept; mechanism of action is unclear
- Mechanism of action needs to be defined
- It was difficult to understand the underlying mechanism of action by which the proposed therapeutic is acting; additional clarity would be helpful in understanding the feasibility of the therapeutic
- Types of EVs responsible for benefits needs to be defined
- The characterization and quantification of EVs is a major challenge
- VEGF/VEGFR mechanism is probably not the only mechanism of action
- Data on EV impact on VEGF was not clearly established
- There is not convincing evidence that the effect is just due to VEGF on EVs
- Timing of treatment and expected mechanism of action is not well elucidated; it is unclear whether EVs can really mediate an effect that lasts days to months
- Additional data are needed to support purported rationale for persistence of effect
- EVs are likely eliminated relatively rapidly and likely will not have a long term impact

- The ultracentrifugation process as a purification strategy is not translatable to the clinic
- Ultracentrifugation for isolation of EVs is not suitable for clinical use; others methods are available
- Ultracentrifugation is not a scalable method of production - use column chromatography
- The dose of EVs required to treat a patient is very large, and the downstream purification process utilizes gradient ultracentrifugation so scalability will likely be an issue
- The downstream purification that will be utilized for clinical production should be used at this point to ensure that the quality of EVs does not change significantly
- Needs improved manufacturing procedure



Application #	TRAN1-10434
Title (as written by the applicant)	Development of an Effective Mobilizer of Stem Cells
Translational Candidate (as written by the applicant)	A new effective stem cell mobilizer
Area of Impact (as written by the applicant)	Patients with multiple myeloma and non-Hodgkin's lymphoma who need hematopoietic stem cell transplantation
Mechanism of Action (as written by the applicant)	The candidate specifically blocks the interaction of CXCR4 on hematopoietic stem cells (HSCs) and its natural ligand SDF-1a expressed by stromal cells in bone marrow. Disruption of SDF1a/CXCR4 interaction causes the release of HSCs and hematopoietic progenitor cells (HPCs) from the bone marrow into the peripheral circulation.
Unmet Medical Need (as written by the applicant)	There is an urgent need for more effective and affordable stem cell mobilizers. We propose to develop such products that will benefit patients with multiple myeloma and non-Hodgkin's lymphoma.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	<ul style="list-style-type: none"> • Additional binding studies through a panel of receptors & functional studies to further confirm the receptor selectivity • Time-response, dose-response, response of multiple treatments and long-term repopulation studies in mice & autologous transplantation study in dogs • Preliminary toxicity studies(acute/chronic toxicity studies, immunogenicity study et al) & PK study (plasma protein binding, biotransformation et al)
Statement of Benefit to California (as written by the applicant)	Autologous hematopoietic stem cell transplantation (HSCT) is an effective therapy for the blood and bone marrow cancer. The most common indications for HSCT in the U.S. are multiple myeloma and lymphoma, accounting for 52% of all HSCTs. If the candidate is commercialized, it may increase the success rate of HSCT, lower the drug cost, and make the drug treatment more affordable and accessible for patients with multiple myeloma and non-Hodgkins lymphoma in California.
Funds Requested	\$2,945,300
GWG Recommendation	(1-84): Not recommended for funding

Scoring Data

Final Score: 72

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

Mean	71
Median	72
Standard Deviation	5
Highest	75
Lowest	60
Count	14
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	14

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have the necessary significance and potential for impact?	2	8	2
Is the rationale sound?	4	6	2
Is the proposal well planned and designed?	2	4	6
Is the proposal feasible?	4	1	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

- Unmet medical need exists
- Clear developmental approach
- Strong rationale
- Potentially better/more effective product compared to existing treatment
- The proposal has a much stronger pharmacokinetic and safety section compared to the previous review
- The approach has been biologically and clinically validated by a marketed drug (Plerixafor); role of CXCR4 in the mobilization of stem cells is well documented and supported in the scientific literature
- This could provide an additional tool for mobilization of stem cells

- Inexpensive study to run
- Good team proposed
- Strong team

Concerns

- The application did not provide convincing information about why this is a critical unmet need
- The proposed product is unlikely to impact an unmet medical need, as there is already an available therapy (Plerixafor) used for the mobilization of stem cells during HSCT
- Not sufficiently innovative, compared to current state-of-the-art
- Need more evidence that there is a clinical need for a new drug in this area
- Need more evidence there is a competitive advantage with the new molecule
- Insufficient contingency plans - there may be local resources to solve problems but it is unclear whether applicant has special access to them
- Unclear advantage over Plerixafor - although possible, there are no preclinical data supporting advantages (eg lower toxicity profile, lack of G-CSF need, improved quality of HSC population)
- No compelling evidence this is as good or better than current methods
- Need more evidence of short and longer term effects
- If value in this product is related to providing competition with current methods, this method may not be less expensive
- Need to show definitive benefit over Plerixafor before funding can be considered
- The submitter did not explain the greater impact of their drug candidate or one of its derivatives over Plerixafor beyond creating more competition in the market place
- Applicant needs to conduct experiments that demonstrate the superiority of their candidate over Plerixafor
- No strong evidence of benefits over current mobilizing agents
- Define benefits on whether this is a better drug than what exists today and why, ie. better dose responses vs time
- Early vs late engraftment needs to be considered
- Applicant should address possible cardiac toxicity effects



Application #	TRAN2-10449
Title (as written by the applicant)	Development of a Noninvasive Prenatal Test for Beta-Hemoglobinopathies for Earlier Stem Cell Therapeutic Interventions
Translational Candidate (as written by the applicant)	A noninvasive prenatal screening test for β -thalassemia and sickle cell disease
Area of Impact (as written by the applicant)	Our test is safer and can be conducted earlier than the current methods of prenatal testing (chorionic villous sampling and amniocentesis)
Mechanism of Action (as written by the applicant)	Our test uses next generation sequencing to analyze fetal DNA in a mother's blood in order to screen for β -thalassemia and sickle cell anemia. Counting sequence reads and comparing observed and expected values for the β -globin mutations allows the inference of fetal genotype. If the test is negative (fetus unaffected), the mother will be spared the invasive testing. If the test is positive (fetus affected), confirmatory testing can be pursued and stem cell therapeutic interventions considered.
Unmet Medical Need (as written by the applicant)	The availability of a safer and earlier fetal diagnosis, such as that afforded by our NIPT assay, will remove a critical bottleneck and greatly facilitate hematopoietic stem cell (HSC) transplants, currently the only curative therapy for the hemoglobinopathies.
Project Objective (as written by the applicant)	Assay ready for validation in CLIA-certified lab
Major Proposed Activities (as written by the applicant)	<ul style="list-style-type: none"> • Optimization of NIPT assay for autosomal recessive disorders and establishing cut-offs to develop an algorithm and software • Testing of performance characteristics to demonstrate analytical sensitivity, specificity, precision, and repeatability adequate for intended use • Demonstration of analytical accuracy on well characterized clinical samples and development of a clinical validation plan that meets CLIA requirements
Statement of Benefit to California (as written by the applicant)	California boasts one of the most ethnically diverse populations of the United States. The incidence of mutations causing diseases such as sickle cell disease, alpha-thalassemia, and beta-thalassemia, per 100,000 infants screened in California are 15.2, 11.1, and 1.8, respectively. As curative therapies involving stem cell transplants and gene editing become more readily available (after birth and intrauterine), earlier and safer fetal diagnosis will be critical for their implementations.
Funds Requested	\$1,721,808
GWG Recommendation	(1-84): Not recommended for funding

Scoring Data

Final Score: 70

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

Mean	68
Median	70
Standard Deviation	11
Highest	75
Lowest	30
Count	15
(85-100): Exceptional merit and warrants funding, if funds are available	0
(1-84): Not recommended for funding	15

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion

influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have the necessary significance and potential for impact?	4	4	5
Is the rationale sound?	4	3	6
Is the proposal well planned and designed?	2	5	6
Is the proposal feasible?	6	3	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 diagnostic is a novel and innovative concept
- Innovative proposal
- Interesting technology, potential for uses other than the one that is targeted
- Such a methodology will enable early detection of hemoglobinopathies

- Novel, non-invasive assay method
- There is a benefit to having a non-invasive alternative to amniocentesis
- The non-invasiveness of the assay is a strength of approach
- A non-invasive procedure is a strength as the risk of amniocentesis is substantial
- Non-invasive nature of test is attractive
- Development of a non-invasive test

- The scientific and clinical rationale are sound
- The project can achieve goals in the proposed timeline

Concerns

- Unlikely to have a major impact on treatment of these diseases
- Not clear that in utero transplants offer a benefit versus performing a transplant after birth
- There is limited value knowing disease status vs potential therapeutic options available for beta thalassemia; you can test a new born and obtain data that is not less valuable - so the value of the test is questionable
- There is concern whether in utero transplants are too high risk and really feasible in the near future
- It is a little too early to assess the potential impact of this test as intrauterine HSC transplants are not clinical practice and have not been demonstrated to be an effective method; until such time, the value of early detection is limited
- It may be useful to provide a survey of how frequently this would be used in the field if the test were available

- Current Target Product Profile should be at least as good as standard of care
- Would like to see a comparison between NIPT vs current methods
- The target profile of the test itself should be 'tighter'; namely much better specificity of the test is required
- The application did not provide convincing data that the diagnostic would be sensitive enough to warrant regular clinical use
- The NIPT approach should be at least as specific and sensitive as current methods (CVS, amniocentesis); specificity of 70% is unacceptable
- Accuracy might not be high enough
- Poor sensitivity of assay due to lack of circulating DNA is a concern
- Need to strengthen data, especially when getting to low level of fetal fraction; accuracy dropped to 70% on the low end of the fetal cell content

- Limited amount of preliminary results
- More data needed with appropriate test samples

- More data needed with regards to the accuracy of the method, specificity of the method, and reliability of the ratio of fetal cells in the blood
- Insufficient proof of concept data with "real samples"
- Ability to accurately call the fetal genotype when fetal fraction is low is not adequately addressed; this needs to be experimentally addressed using the prototype assay using real world samples, especially when maternal and fetal alleles are shared
- The proposal is not supported by a lot of data; team has used contrived samples to evaluate ability to capture short fragments, limit of detection, estimation of minor fraction etc.; so far they have used only 20 actual patient samples to establish proof of concept
- To establish proof of concept, failure rates, and demonstrate quantitative nature of NIPT approach: many more samples with varying amounts of DNA across multiple ethnicities are necessary, ensuring several instances where shared alleles between mother and fetus can be tested
- Mitigation strategies for experimental variation in SNP data resulting in inaccurate fetal fraction estimates is not adequately addressed; this has to be experimentally addressed using the prototype assay using real world samples
- \$1.2 million is a lot of expense for turning a prototype assay into a laboratory developed test



Application #	TRAN1-10413
Title (as written by the applicant)	Retinal Progenitor Cells for Treatment of Diabetic Retinopathy
Translational Candidate (as written by the applicant)	Human retinal progenitor cells (RPCs)
Area of Impact (as written by the applicant)	Use of retinal progenitor cells in diabetic retinopathy; scale up manufacturing of clinical product
Mechanism of Action (as written by the applicant)	The mechanisms of action are neurotrophic preservation and potential reactivation of neuronal retinal cells, as well as enhanced vascular integrity to improve circulation and minimize leakage.
Unmet Medical Need (as written by the applicant)	Diabetic retinopathy (DR) is treated by anti-VEGF agents, steroid injections, laser, etc. However, the important neural degeneration component of DR is not addressed by any current therapeutic option. RPCs are intended to provide neuroprotection and increased vascular stability in patients with DR.
Project Objective (as written by the applicant)	Pre-IND meeting with FDA
Major Proposed Activities (as written by the applicant)	<ul style="list-style-type: none"> • cGMP process scale up development and analytical assay development/qualification at industrial grade GMP facility (CMO). • Proof-of-Concept (POC) non-clinical study to test retinal progenitor cells as method of treating diabetic retinopathy in rat model of the disease. • Pre-IND meeting with the FDA to discuss optimal pathway to enter into clinical trials with our therapeutic candidate.
Statement of Benefit to California (as written by the applicant)	The direct benefit is medical in that there is currently inadequate treatment for the large number of Californians that suffer from diabetic retinopathy, many of whom are of working age. DR impacts all populations, most severely underserved groups. Furthermore, success in a prevalent condition like DR would boost the biotechnology sector of the economy in California, thereby providing a host of indirect benefits.
Funds Requested	\$4,741,411
GWG Recommendation	<i>(1-84): Not recommended for funding</i>

Scoring Data

Final Score: --

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

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

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have the necessary significance and potential for impact?	4	1	5
Is the rationale sound?	2	6	2
Is the proposal well planned and designed?	0	5	5
Is the proposal feasible?	0	3	7

Reviewer Comments

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

Strengths

- Diabetic retinopathy is a serious condition that would possibly benefit from a stem cell based product
- There is a pressing need for a novel treatment
- Retinal Progenitor Cells (RPCs) are already in an existing clinical trial
- Applicant provides good preliminary data
- Applicant already has a good animal model
- The group is well-experienced

Concerns

- The current treatment protocols (laser, anti-VEGF) are effective and any replacement will need quite significant benefits beyond this
- It is unclear that neuroprotection will have significant functional benefits in humans with diabetic retinopathy
- It is unclear whether this therapy would be beneficial, and would be better/more effective than current therapies
- Unclear how the therapy can be delivered early enough, before the neurodegeneration already has occurred
- The animal model allows the cells to be administered shortly after induction of the diabetic state, which may not be possible or practical in patients.
- In study 3, the cells were injected prior to disease onset; this doesn't help determine efficacy
- It is unclear whether the applicant considered the role of vascular damage of the disorder
- Vasculopathy is a major problem in diabetic retinopathy. It is unclear why this aspect of the disease is not targeted
- The approach only targets neurodegeneration, while vascular changes are not addressed
- The proposed mechanism of a neuro-regenerative effect was not clearly explained or supported by convincing data
- The mechanism of action is very unclear
- It is unclear whether the retinal progenitor cells, which have been used in cell replacement work, will have a paracrine effect
- The paracrine effects of RPCs need much better proof of efficacy
- There is a lack of convincing proof of concept data to show that cells are neuroprotective
- If the RPC are not to be utilized in the same manner as is in the existing clinical trial, a strong comparability study should be considered



Application #	TRAN1-10567
Title (as written by the applicant)	Therapeutic development of Oxy200, an oxysterol with bone anabolic and anti-resorptive properties for intervention in osteoporosis
Translational Candidate (as written by the applicant)	A novel oxysterol with bone anabolic and anti-resorptive activity that will effectively and safely treat osteoporosis better than current options.
Area of Impact (as written by the applicant)	Osteoporosis that results in bone fractures
Mechanism of Action (as written by the applicant)	The proposed candidate will target Mesenchymal Stem Cells in the skeleton to stimulate their differentiation into bone forming osteoblasts that will rebuild the bone lost to the disease. In addition, the candidate will exert anti-resorptive effects due to presence of the bisphosphonate Alendronate that inhibits bone resorption. The candidate is an orally administered treatment that is designed to be delivered to bone.
Unmet Medical Need (as written by the applicant)	The candidate fills a gap in bone anabolic agents for the treatment of osteoporosis. Currently only two FDA approved anabolic agents are available, both of which have limited use due to significant safety concerns and patient non-compliance due to daily subcu injections that cause adverse effects.
Project Objective (as written by the applicant)	Initiate IND enabling studies, and Pre-IND meeting
Major Proposed Activities (as written by the applicant)	<ul style="list-style-type: none"> • Scale up of candidate compound, Oxy200 • Determination of optimum dosing and pharmacokinetics • Toxicology studies
Statement of Benefit to California (as written by the applicant)	MAX BioPharma's program has the potential to have a significant positive impact on the lives of patients with osteoporosis, especially in California where its unique demographics make it particularly vulnerable. Latinos are 31% more likely to have osteoporosis than Caucasians, and California has the largest Latino population in the US, accounting for 39% of its population. Data suggests hip fracture incidence has increased among Latinos from 1983 to 2000, while it fell among non-Latino women.
Funds Requested	\$1,757,830
GWG Recommendation	<i>(1-84): Not recommended for funding</i>

Scoring Data

Final Score: --

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

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

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have the necessary significance and potential for impact?	7	3	2
Is the rationale sound?	2	6	4
Is the proposal well planned and designed?	0	11	1
Is the proposal feasible?	1	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

- Major unmet medical need
- The need is great for anabolic agents
- There is a definite need for new agents to treat post-menopausal osteoporosis
- This is an interesting approach and there is a decent rationale for this target
- Novel concept
- Unique approach to osteoporosis
- Approach of targeting to the bone is attractive
- Clever construct
- Good program of preclinical studies
- Sound safety, drug metabolism and pharmacokinetic approach after the clinical candidate is identified
- Good team

Concerns

- Animal models need to be redesigned to improve the study
- Several of the studies were not designed correctly
- Potential benefits not addressed adequately
- Alendronate must be added to the preclinical in vivo trial--the apparent efficacy of Oxy200 could conceivably be due to alendronate alone
- Comparative benefit over alendronate would provide support for reapplication
- There is not enough data on showing a significant anabolic effect - especially with a combination therapy where the anabolic effect may be inhibited
- Additional pharmacology studies are needed to demonstrate the utility of combination therapy
- Studies demonstrating positive bone selectivity, plasma stability and bioavailability are needed
- The application does not fully address safety issues that might arise from conjugation to alendronate
- Long term follow-up is needed; brittle bones are a concern
- A realistic safety profile needs to be developed with regards to osteonecrosis of the jaw and atypical femur fractures
- Applicant needs clinical input
- Clinical design needs work
- Some of the studies (hERG, Ames) were being done at the GLP level, which is too early in the program
- Expertise in formulation is lacking
- This program seems early for funding under this call; the project looks more like a lead optimization program
- There should be a single candidate
- It is unclear whether there are one or two candidates
- Identification of a defined clinical candidate is required
- Errors in T scores in Target Product Profile
- Errors in the write-up on the proposal



Application #	TRAN1-10624
Title (as written by the applicant)	Pre-clinical development of a small molecule for the treatment of osteoarthritis
Translational Candidate (as written by the applicant)	A novel small molecule drug candidate, 423F
Area of Impact (as written by the applicant)	423F will be targeted to prevent the advancement of, or reverse, osteoarthritis
Mechanism of Action (as written by the applicant)	423F activates a patient's own cartilage stem/progenitor cells, helping them to repair cartilage damage. It also makes these cells more resistant to degenerative signals, thus interrupting the disease cycle. These changes in the joint should reduce pain and increase mobility in treated patients.
Unmet Medical Need (as written by the applicant)	25 million adults suffer from osteoarthritis. Beyond reducing pain, there are no current treatments that slow or stop the progression of osteoarthritis. 423F could become the new standard of care by slowing or reversing OA, positively impacting the lives of millions of adults.
Project Objective (as written by the applicant)	Pre-IND meeting
Major Proposed Activities (as written by the applicant)	<ul style="list-style-type: none"> • Rodent studies to determine dosage amount and formulation • Toxicity and tumorigenicity studies in rodents to verify safety of the drug • Testing dosages of 423F in a dog model of OA and verifying that it is not toxic
Statement of Benefit to California (as written by the applicant)	5.9 million Californians suffer from some form of arthritis. Currently, treatments for osteoarthritis focus on pain management, only treating the symptoms of the disease. 423F activates cartilage stem/progenitor cells, making them resistant to degenerative signals and helping them repair cartilage damage. Therefore, 423F will be the first treatment to interrupt the disease cycle in OA, potentially changing the lives of millions of Californians by reducing pain and increasing mobility.
Funds Requested	\$2,837,604
GWG Recommendation	<i>(1-84): Not recommended for funding</i>

Scoring Data

Final Score: --

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

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

Score Influences

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

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have the necessary significance and potential for impact?	6	7	1
Is the rationale sound?	3	9	2
Is the proposal well planned and designed?	1	12	1
Is the proposal feasible?	1	9	4

Reviewer Comments

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

Strengths

- Huge unmet medical need
- Significant disease target
- Addresses important, common clinical problem

- Fascinating pathway--anti-inflammatory and pro-regenerative
- Small molecule-attractive approach
- Persuasive therapeutic concept
- Extensive efficacy preliminary data
- With some exceptions, the proposal has a strong preclinical rationale

- Investigator addressed previous reviewer concerns
- Responded very well to previous critiques

Concerns

- Narrow benefit/risk profile demands outstanding safety package
- Risk of tumors and other off-target effects may be greater than the benefit of reducing of OA
- Tumorigenicity - must have outstanding toxicity package before considering potential efficacy; the benefit-risk profile is very narrow
- For a chronic disorder, must have strong support of preclinical safety prior to proceeding w/ various preclinical efficacy in vivo studies
- Safety profile needs to be defined; product may be tumorigenic
- Safety concerns are significant - especially tumor potential
- Concerned that studies as currently designed will not provide for early de-risking of tumorigenicity
- The proposed target has significant safety issues associated with it; specifically, there is concern with the potential tumorigenicity associated with the target
- The data submitted does not suggest that the benefits outweigh the risks of increasing MYC expression with this product
- The MYC accumulation and the specter of malignancy are concerning
- Choice of target indication is not strong without accompanying toxicity data
- Insufficient preclinical toxicity studies
- Toxicity studies not focused the actual intended final product
- Major concerns about toxicology and use of appropriate animal models
- The injections of the compound in young animals and soon after the induced damage likely provides a softer efficacy target than an aged patient with other co-morbidities
- Better animal models should be developed to test the product; it is unclear the cell population responsive to the therapeutic compound will be available in older patients
- The animal model does not reflect the age of the intended human recipients and should be changed
- It will be important to provide information that the positive control will be positive in the osteosarcoma xenograft model
- The proposal to develop similar compounds with different formulations may provide a work around if the lead compound proves to be unsafe, but at considerable cost and time since they would be starting over